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

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THYROID FUNCTION POST SUPRACLAVICULAR LYMPH NODE IRRADIATION IN PATIENTS WITH BREAST CANCER

By

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A dissertation submitted in Partial Fulfillment of the Requirements for the Degree of Master of Medicine (Clinical Oncology) of the Muhimbili University of Health and Allied Science

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for examination of dissertation entitled "**THYROID FUNCTION POST SUPRACLAVICULAR LYMPH NODE IRRADIATION IN PATIENTS WITH BREAST CANCER"** in fulfillment of the requirement for the Master of Medicine in Clinical Oncology of Muhimbili University of Health and Allied Sciences.

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Date____________________________

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Dr. Nazima Dharsee
(Supervisor)

Date____________________________

DECLARATION AND COPYRIGHT

I, **Fidel Rubagumya**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature…………………………………… Date……………………………………...

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I acknowledge the contribution of every one in development of my proposal, data collection, analysis and report writing, especially fellow residents who always challenged me and ORCI staffs in general.

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DEDICATION

First and foremost, I dedicate this work to Almighty God who enables me to do all I do.

I lovingly dedicate this dissertation to my mother late **Christine MUKABAGORORA** who was and continues to be an inspiration and encouragement to me.
May your soul rest in eternal peace Mom.

I dedicate this work again to my family: my Dad, brothers and sister who have always believed in me.

ABSTRACT

Background

Breast cancer remains the most common cancer in women worldwide and across Africa in particular. In East Africa, the estimated incidence of breast cancer comes second only to cervical cancer. Supraclavicular irradiation post modified mastectomy is a crucial component of breast cancer management; it improves local control and overall survival. This is however associated with adverse effects including thyroid dysfunction which is usually under-reported.

Aim

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 who were recruited from May 1, 2017 and subsequently followed up until May 30, 2018 at ORCI. Descriptive statistics were used to report patient demographics, disease characteristics. Pretreatment TSH, fT4 and fT3 values were compared with the corresponding values obtained after treatment by Wilcoxon signed-rank test.

Results

A total of 42 patients were recruited for this study with a mean age of 55.7 (32-71) years. The mean for baseline TSH level was 2.90(±6.37) while that for T4 and T3 were 15.77(±4.83) and 3.46(±6.22) respectively. A Wilcoxon signed-rank test indicated that there was a statistically significant rise in mean TSH level at baseline compared to those at 3, 6 and 9 months post treatment with p-values of 0.0047, 0.0002 and less than 0.0001 respectively. The difference between baseline mean levels for T3 and T4 was statistically significant both at month 6(T3, p=0.0028; T4, p=0.0018 and month 9(T3, p=0.009; T4, p=0.0001) of follow up respectively. Subclinical HT was found in 10% of the patients.

Conclusion

As it was hypothesized, there was a trend towards subclinical HT and these results reflect the

necessity to routinely evaluate thyroid function in patients treated with radiation to the supraclavicular region.

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LIST OF ABBREVIATIONS

T3: Triiodothyronine

T4: Thyroxine

TSH: Thyroid stimulating Hormone

TRH: thyrotropin releasing hormone

HT: Hypothyroidism

RIHT: Radiation Induced Hypothyroidism

LABC: Locally advanced breast cancer

LR: Local Recurrence

SC: Supraclavicular

SCLN: Supraclavicular Lymph Node

3D-CRT: Three-Dimensional Conformal Radiotherapy

2D: Two-dimensional

RT: Radiotherapy

ECOG: Eastern Cooperative oncology group

IRB: Institutional review board

ORCI: Ocean Road Cancer Institute

LIST OF TERMS

Breast cancer

Radiotherapy

Hypothyroidism

Supraclavicular

Lymph Nodes

CHAPTER I: INTRODUCTION

I. Background

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) in the supraclavicular (SC) nodes [1]. The routine post-operative irradiation of breast cancer patients involves irradiation of the breast or chest wall for patients who underwent mastectomy, ipsilateral SC and internal mammary nodes conventionally with 50 Gy /25 fractions [2].

Concerning radiation induced thyroid dysfunction, many studies have been conducted on the effects of radiation therapy on thyroid function in patients with head and neck cancers; a group in which the whole thyroid gland is in the radiation field [3].However, few studies also showed that SC nodal irradiation in patients with breast cancer where unknown portion of thyroid is in the radiation field was associated with a higher incidence of hypothyroidism (HT) and reduction in the size of the gland [1].

It is important to note that supraclavicular irradiation is located in the same axial plane as the thyroid gland. However, little is actually known about how much radiation the gland receives. Studies suggest that doses between 26Gy-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 HT were not included [6]. 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 the development of radiation induced HT, has been determined.

RT induced hypothyroidism has been reported at different periods after radiotherapy treatment involving the thyroid gland and this ranges from 3 months to 20 years [9,10, 11]. As a result, some clinical protocols recommend routine follow up of thyroid hormones 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 technologywith three-dimensional conformal RT (3D-CRT), which is able to delineate the thyroid gland as organ at risk (OAR).

In a study by Akın M and colleagues, it was found that 44% of the 122 breast cancer patients who were treated with 3D CRT planning, the thyroid gland was exposed to considerable doses which put these patients at risk of developing thyroid abnormalities [14]. Ahmad M. Alhosainy and colleagues compared the effect of two different planning system (2D vs. 3D CRT) and they found that the 3D conformal radiotherapy technique of supraclavicular nodal irradiation is superior to 2D conventional radiotherapy technique in case of breast cancer patients and regarding the impact on thyroid function [1]. Akyurek S and colleagues found that Supraclavicular RT in patients with breast cancer appear to amplify the risk of HT [13].

II. Literature review

Breast cancer remains the most common cancer in women worldwide and in particular in Africa [15]. In East Africa, the estimated incidence of cervical cancer appears higher than that of breast cancer [15]. Breast cancer is an issue of public health concern in Tanzania [16]. It ranks third after cancer of the cervix and Kaposi's sarcoma and it accounts 9.3% of all cancers seen at Ocean Road Cancer Institute (ORCI) [17]. Due to different factors, both medical and social, patients in Sub Saharan Countries present to hospitals at late stage. Studies have shown that, women with stage III and IV disease made up 77% of patients with breast cancer at Mulago Hospital in Uganda [18]; 77% of patients at Butaro Cancer Center of Excellence in Rwanda [19]; and 78% of breast cancer patients at the Angolan Institute of Cancer Control [20].

Stage III and IV or otherwise locally advanced breast cancer implicates involvement of the disease in the regional lymph nodes including those in the axilla and supraclavicular regions [19]. There is strong evidence for a substantial reduction in local or regional recurrence and subsequent increases in the disease-free survival rates when post-mastectomy radiation therapy to the chest wall and the regional nodal areas is administered [20]. In other developed countries, it has been shown that the irradiation of the supraclavicular region in patients treated for breast cancer involves the thyroid gland and can induce hypothyroidism [21].

The thyroid gland is the largest endocrine gland in human [22]. This gland secretes two hormones, triiodothyronine (T3) and thyroxine (T4) that play a big role in normal growth and development, general body energy expenditure and substrate utilization [23, 24]. Thyroid hormones can be deranged by many factors. These can include diseases that affect the thyroid, nutrition deficiencies and indirect or direct irradiation of the thyroid gland during treatment of cancers.

Cancer management has a multidisciplinary approach and different modalities are used to treat cancer. These include surgery, chemotherapy and radiation therapy. It is estimated that more than fifty percent of cancer patient will need radiation therapy as a partial or sole treatment modality [25].

Radiation effects on the thyroid gland were first reported in 1920s [24]. The type of hypothyroidism that results from irradiation of the thyroid gland is called primary hypothyroidism and this can be clinically overt which is characterized by biochemical findings of low free T4 and high TSH or subclinical which is common with normal fT4 and high TSH [1]. Subclinical thyroid dysfunction, which can be diagnosed by thyroid function, is more frequent but is often missed because routine testing of thyroid hormones is not done during follow-up at Ocean Road Cancer Institute.

Consequences of subclinical hypothyroidism are not very well known, most of the literature refers to adverse consequences such as cardiac dysfunction, adverse cardiac end points, including atherosclerotic disease and cardiovascular mortality, elevation in total and low-density lipoprotein, systemic or neuropsychiatric symptoms, and progression to clinical hypothyroidism. [26,27,28,29]

There are several proposed mechanisms of radiation-induced hypothyroidism. Radiotherapy-induced thyroid dysfunction is caused by damage to small thyroid vesselsand to the gland capsule [24,30]. Radiation induced atherosclerosis of the carotid artery may also result in relative ischemia of the thyroid gland [30]. There is evidence confirming the vascular cause of thyroid injury [31]. It is rare that a deficiency of iodine due to poor dietary habits, prolonged nasogastric tube feeding or fistula formation may lead to hypothyroidism [24]. Other mechanisms include direct thyroid cell injury from radiation and probably immune-mediated damage [32,24,33,34]. It has been suggested that the late-onset injury is caused mainly by vascular damage, whereas acute effects result from parenchymal cell damage [35]**.** In a study by Ahmad M. Alhosainy, 65% of his patient had a reduction in thyroid gland size post-supraclavicular radiation [1].

While most of these studies were done in developed countries, with newer radiation techniques, little is known about the magnitude of adverse effects that old technologies have on the thyroid gland. Greater magnitude and prolonged duration of TSH elevation increase the probability of progression to clinical hypothyroidism and therefore increase the potential benefit of treatment of subclinical hypothyroidism. Recognizing subclinical hypothyroidism at an early stage can hence prevent clinical hypothyroidism and its attendant morbidity. [36]

After reviewing several studies, it is evident that there is lack of studies on the effects of radiation therapy on thyroid gland function secondary to treating supraclavicular lymph nodes. This dearth of data is especially profound in low-income settings where the old radiation machines (cobalt 60) and planning system like two dimensional (2D) are still in use. RT-induced hypothyroidism has remained under estimated and under reported, because routine assessment of thyroid function is not done during follow-up, resulting in failure to detect and treat a reversible cause of morbidity for a significant proportion of surviving patients. [37]

Hence, the purpose of this study was to identify the magnitude of hypothyroidism, following RT to the supraclavicular lymph node region, to assess the mean time period for the development of hypothyroidism, usefulness of TSH, T3, total T4, in identifying and treating patients with subclinical thyroid dysfunction, and to stress upon the necessity of including thyroid function tests as part of follow-up.

III. Problem statement

The number of breast cancer cases continues to rise in Sub-Sahara Africa and most cases are locally advanced with a high risk of recurrence. These cases present with large tumors, node involvement, and predominantly young patients of 40-60 years. Radiation therapy to the chest and ipsilateral supraclavicular lymph node (SCLN) region becomes inevitable in this patient population.

The old radiotherapy machines and treatment planning system, which are no longer used in developed countries, are still being used in developing countries including at ORCI where cobalt 60 is being used. This is mainly because of lack of capacity to run and maintain the functionality of linear accelerators but also infrastructures like consistent electricity supply necessary to manage these new radiotherapy technologies. The delicacy involved with the new technologies means that the old radiotherapy technologies will still be used for some years either as a stand-alone or back up where the new 3D ones are available.These old machines (cobalt 60) with two-dimensional planning system have several limitations, including the inability to limit radiation to targeted area only but rather includes even normal tissues. While thyroid gland is not considered as OAR when treating supraclavicular region in patients with breast cancer, it receives substantial radiation doses and if it’s tolerance is exceeded hypothyroidism can develop and in a long run thyroid cancer.

Despite the increasing number of cancer cases, and for breast cancer in particular, it has been shown in the literature that no studies have been done to document the side effects of SCLN region radiation to non-target organs like thyroid gland in low resource settings. The lack of knowledge of how much critical organs are irradiated during breast cancer treatment puts these patients to unknown risk either for acute or long term. This study, which to our knowledge was the first of its kind in Sub-Sahara Africa and Tanzania in particular, provides knowledge on effects of radiation on thyroid gland and suggests measures to be devised in minimizing radiation side effects while optimizing the treatment of target areas.

IV. Rational

Breast cancer continues to be the most prevalent cancer and the most common cause of cancer related deaths in women in sub-Saharan Africa. Due to lack of knowledge about this disease in the general population, most patient present with high risk advanced diseases. The advanced breast cancer requires multiple modalities of treatment and this includes radiation therapy to the chest wall and supraclavicular lymph node.

The use of radiation therapy in treating breast cancer has been in existence for a long time and in developed countries new technologies has been invented that try to spare the normal tissues while subjecting more radiation to the diseased tissues. However, most Sub-Saharan African countries still use the outdated technologies that expose the normal tissues to the same amount of radiation as the tumors.

The results of this study provide new knowledge to ORCI and the rest of centers in developing countries that still use the old technologies on how much effect radiation has on the thyroid gland while treating the supraclavicular lymph nodes in breast cancer patients. As ORCI is gradually transitioning to using LINAC machines with 3D planning, the results of this study will be used to advocate for prioritizing breast cancer as one of diseases to be treated using the new technology in a move to protecting the gland during treatment. This will prevent the acute and long-term side effects, such as asymptomatic and symptomatic hypothyroidism. In addition, the results of this study help to stress the need to include follow up of thyroid functions in the treatment protocol of breast cancer patients at ORCI and all cancer centers in Tanzania.

V. Research Question

Does supraclavicular lymph node irradiation in patients with breast cancer, using cobalt 60 machine and 2D planning, increase the risks of developing hypothyroidism?

VI. Objectives

i. General Objective

To evaluate radiation induced thyroid gland functional changes following treatment of supraclavicular lymph nodes in breast cancer patients.

ii. Specific objectives

1. To document the disease characteristics of breast cancer patients receiving radiation at ORCI.
2. To describe the socio-demographic characteristics of patients with breast cancer treated at ORCI.
3. To describe treatment modalities used in treating patients with breast cancer at ORCI
4. To determine the thyroid gland hormonal changes following irradiation of SCLNs

CHAPTER II: METHODS

I. Study Design:

This was a prospective cohortstudy to determine changes in the thyroid functions following postoperative chest wall and supraclavicular lymph node radiation.

II. Study Setting

Ocean Road Cancer Institute is cancer referral facility, located along the Indian Ocean within the Capital City of Tanzania, Dar es Salaam. The health facility is one of the oldest health institutions in Tanzania, founded in 1895.The cancer care started in 1980 when the Radiotherapy Unit of the Faculty of Medicine, University of Dar es Salaam was shifted from Muhimbili Medical Centre to the Ocean Road Hospital. In 1996 the center become autonomous and was upgraded to a national referral facility for comprehensive cancer services accessible by all Tanzanians and patients from neighboring countries. The center offers cancer prevention and screening programs, radiation therapy, medical oncology, and palliative care.

III. Study Population:

A total of 42 patients with a diagnosis of breast cancer treated with supraclavicular lymph node region irradiation were enrolled from May 1, 2017 and subsequently followed up until May 30, 2018 at ORCI.

i. Inclusion Criteria

- All patient with confirmed breast cancer diagnosis and eligible for radiation therapy, including SCLNs
- Patient enrolled in cancer care and treatment at the ORCI
- Patients being treated with curative intent
- Patients with ECOG status of 0-2 or better

ii. Exclusion Criteria

Patients were excluded if they fell into the following categories

- Male patients
- Patients with primary thyroid disease.
- Previous thyroid surgery
- Previous neck treatment with radiotherapy that included hypothalamic pituitary axis or neck.

IV. Sample Estimation

A population prevalence formula was used to determine the sample size needed for this study:

$$\frac{Z^2(P)(1-P)}{d^2}$$

Using Z score of 1.96 for a confidence interval of 95% and assuming a population prevalence (P) of 44% [29], a sample size of 42 patients would provide 15% precision (d) for overall prevalence of thyroid dysfunction within one year of radiation to the supraclavicular nodal region. We therefore aimed to recruit 45 patients for this study.

V. Sampling procedure

All patients with a diagnosis of breast cancer presenting at ORCI and fitting the inclusion criteria were enrolled until the above-mentioned sample size was reached.

VI. Data Collection

Using data abstraction form, data ranging from patients' identifications, disease characteristics, patients' characteristics, stage of the disease, surgery type, chemotherapy regimen used, radiation therapy and other details were extracted from patient's files.

VII. Radiotherapy

Cobalt machine and 2D technique was used in treating this cohort of patients. Clinical and radiological landmark borders of the fields was determinedfor the supraclavicular lymph node region radiation field. The borders of this single anterior-slightly oblique field were the following; a skin flash of about of about 0.5-1.5cm superiorly, inferior border at the lower border of the ipsilateral clavicular head, medial border at the lateral midline 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 to match with the chest wall tangent field. The dose to the SC nodes was prescribed to a depth of 3 cm.

The chest wall and SCLN region each received 50Gy of radiation given in twenty-five fractions. The dose and radiation fields used were as detailed in the Ocean Road Cancer Institute protocol and clinical radiation oncology by Gunderson et al [38,39]

VIII. 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.Patients were asked to use either of the two accredited laboratories that use same reference ranges and the references values 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 the fact that clinical hypothyroidism was not expected at a short follow up, a diagnosis of HT was solely based on biochemical thyroid hormones. Subclinical HT was TSH values beyond normal values provided by the laboratory and/or fT3 and/or fT4 values lower than the minimum value provided by the laboratory.

IX. Data Analysis

Data was entered into Excel and analyzed using STATA version 13. Pretreatment TSH, fT4 and fT3 values were compared with the corresponding values obtained after treatment by Wilcoxon signed ranks test. A P values < 0.05 was considered significant. Variables like histology, hormonal status, disease stage, total dose were descriptively reported.

X. Data Security

A dataset key was created assigning a unique identifier to each enrolled patient for recording individual patient study data. Resultant study data were de-identified and stored electronically. The study investigator was responsible for overseeing data management. All paper-based study data were stored in locked cabinets during study period and were shredded and disposed appropriately after the study was completed. Electronic study data/databases were stored in password-protected files on an encrypted computer. Data access was only to principle investigator and the supervisor. Only de-identified data untraceable to study participants was retained after study completion by the study investigator. De-identified data may be shared with ORCI OR MUHAS leadership and regulatory bodies as may be required for oversight.

XI. Ethical considerations

Written informed consent to participate was obtained from patients. The approved consent document detailing the purpose of the study, risks and benefits of the research were reviewed orally with participants in Swahili.

Care was taken to ensure that patients were aware that they could refuse participation in the study, or discontinue the study at any time once they had started, and that neither would affect the medical services or other care that they received at ORCI. This was clearly conveyed as part of the consent process and expressed in the informed consent document. Study approval was sought from MUHAS institution review board (IRB) before enrolling the patients.

CHAPTER III: RESULTS

Table I: Patients Characteristics

Variables	All patients (n=42)
Age	
Mean	55.7
Range	32-71
Histology	
IDC	42
Stage	
I	1
II	3
III	38
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: Perineuralinvasion; LN: Lymph nodes

Patients' characteristics are summarized in ***Table I.*** The mean age of the patients was 55.7 (32-71) years. Regarding tumor stage and biology ,90 % of the patients had Stage III, 38 % were Grade II while 36 % were Grade III, 69% were ER+ and only 24 % were HER2. 22 patients (52%) had left breast cancer. Regarding other prognostic factors that warranted radiation post 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) harvested lymph nodes were 6.75(±4.3).

Table II: 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
Site treated with Radiotherapy	
Breast/Chest wall	50
Supraclavicular	50

C: Cyclophosphamide, A: Adriamycin, F: Fluorouracil, T: Taxane

Table II shows different treatment modalities, 98 % underwent modified radical mastectomies while only one patient got breast-conserving surgery. Most of the combination chemotherapies given were anthracycline based, 55 % being TAC regimen and 29 % being AC-T regimen. These chemotherapy regimens were given in 76% of patients as adjuvant following a pattern of Surgery-adjuvant chemotherapy –Radiation. Among the ER + patients 53% got Tamoxifen while 21% got anastrozole.Two patients who were ER+ did not get Tamoxifen/anastrozole.

All recruited patients got 50Gy in 25 fractions with 2Gy per fraction 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 and was thus not able to continue follow up. Three (7%) patients did not show up for their ninth month follow up, howeverthe analysis included all 42 patients. Of the 42 patients, 10% developed subclinical HT and this was detected biochemically on the ninth month of follow up.

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

	Baseline	3months	6months	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

The mean for baseline TSH level was 2.90(±6.37) while that for T4 and T3 were 15.77(±4.83) and 3.46(±6.22) respectively [***Table III***]. A Wilcoxon signed ranks test indicated that the risesin mean TSH level between the baseline and those at 3 ,6 and 9 months post treatment was statistically significant with P-values of 0.0047, 0.0002 and less than 0.0001 respectively. The difference between baseline mean levels for T3 and T4 were statistically not significant at month three of follow up (p=0.1225 and p=0.3203 respectively). However, they were statistically significant both at month 6(T3, p=0.0028; T4, p=0.0018 and month 9(T3, p=0.009; T4, p=0.0001) of follow up respectively [***Table IV***].

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

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

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

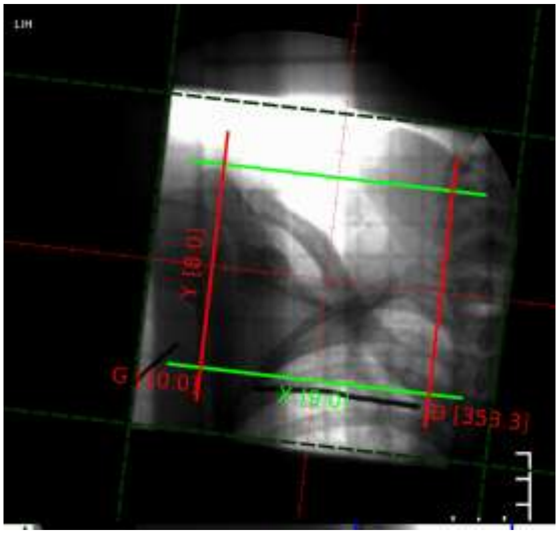

Figure 1A: Digital Reconstructed image of supraclavicular field

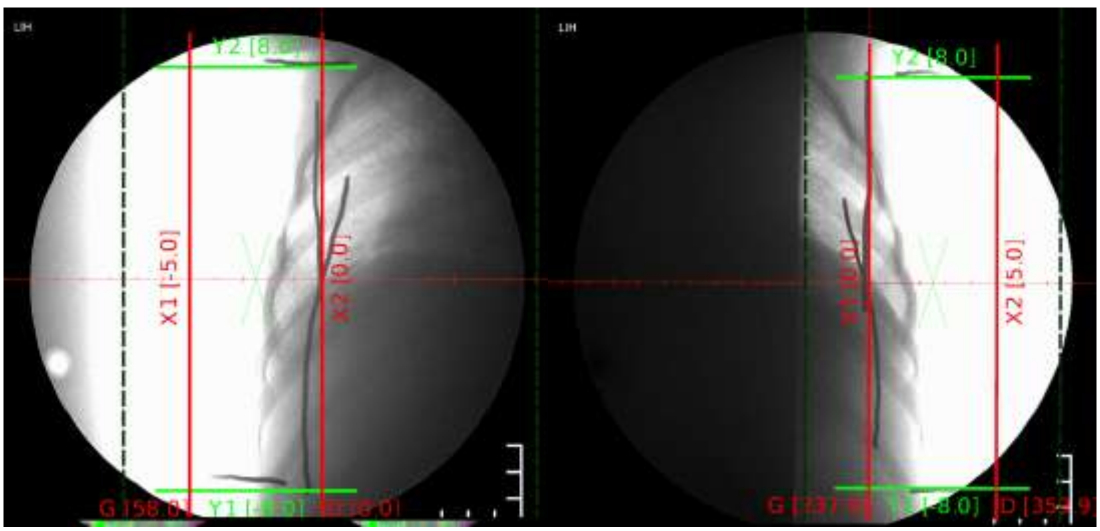

Figure 1B: Digital reconstructed image of the chest wall/tangential field

CHAPTER IV: DISCUSSION

The practice to treat breast cancer, especially locally advanced disease, is to use multimodality therapy. Chemotherapies, targeted therapy and radiation are all used to cure breast cancer patients. For patients who have surgical pathological risk factors (PNI, LVI, Positive LNs, Positive margins) for local recurrences, need to get radiation therapy to improve local control and reduce death [40]. Despite the benefits of radiation therapy in treating breast cancer, there are adverse effects that are associated with this modality of treatment. These side effects are mainly due to normal structures that are included in the radiation field in spite not being the target of treatment. These include the heart, lungs, chest bones and thyroid among others [41]. Current advances in treatment modalities and imaging technologies have made it possible to minimize the size of radiation fields by conforming only to the targeted tumor. These technologies including 3D RT, IMRT, IGRT and brachytherapy are expensive assets and only handful of African countries can afford them [42]. In 2010, a report by International Atomic Energy Agency reported that in Africa, only 23 countries had radiotherapy machines and most of them were concentrated in few countries [42]. In total, these 23 countries had 277 radiotherapy machines (88 cobalt-60 units and 189 linear accelerators). The majority of these machines especially the linear accelerators were concentrated in South Africa (92) and Egypt (76), which together accounted for 60% of the radiotherapy equipment resources in Africa [42]. Evidently, most African countries use Cobalt machines with a 2D planning and lacks the conformity given by the advanced modalities. Radiation induced hypothyroidism (RIHT) is a well-known entity as late developing side effect in patients treated with radiation therapy for head and neck cancers [1,43,44]. Most of these studies however evaluated patients who had been treated with radiation using 3D CRT. The only article that compared 3D versus 2D planning had only 20 patients (10 treated by 2D and 10 by 3D) and showed that 20% of those treated with 2D had subclinical hypothyroidism compared to 10% of those who were treated on 3D [1]. Some studies have reported HT in 40% of patients after 4-5yrs of treatment [45,46]. In our study, the incidence of HT was 10% and this is similar to other studies that reported 6-21% [1,5,943-44].

Both the QUANTEC and Emami that reported on tolerance doses of different organ at risk of radiation did not report anything regarding thyroid gland [46,47,6]. Some studies especially on treatment of head and neck cancer, Hodgkin lymphoma have reported different tolerance doses depending on the volume of thyroid irradiated. Cella et al considered V30 >62.5% as a considerable risk factor to develop HT in Hodgkin's lymphoma [7]. Tunio et al considered V30>50 % as a risk for HT in patients with breast cancer treated with radiation to the SC area [48].

Some studies have tried to correlate the volume on 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 as risk factors for HT [8]. Cella et al confirmed that V30 can be considered a sole predictor of HT [7].

Currently, no study has shown correlation of irradiated volume using 2D planning as it is not possible to know how much volume is irradiated using fluoroscopy. This is shown by ***Figure I A&B***, where the medial border of the supraclavicular radiation field might be including one-third portion of thyroid gland.

In previous studies, of same nature as this one, biochemical hypothyroidism was found in patients who had received anthracycline based chemotherapy and tamoxifen [8,46]. This correlates with our study, all 4 of the patients who had subclinical HT had also received anthracycline based chemotherapy (3 TAC,1 AC-T) and two of them Tamoxifen. A combination of these two medications with radiation to the supraclavicular region increase the chances as showed by Reinertsen et al [4]. According to our knowledge, there is no study in Africa evaluating HT in breast cancer patients post treatment making this the first article to report on status of thyroid functions post supraclavicular lymph node region radiation in resource limited settings.

CHAPTER V: CONCLUSION

The incidence of HT in our cohort was 10%, which is comparable to other studies. Here, the subclinical HT was detected at 9 months of follow up but the was a gradual statistically significant increase of TSH and decrease of both T3 and T4. Given that this was a short follow up, there is a high chance that if these patients are followed over time a larger percentage will develop subclinical and clinical HT. We therefore believe that because of the high risk of developing HT in these patients, thyroid function should be evaluated during follow up visits and further prospective studies should be carried out to confirm incidence of hypothyroidism in this patient population in Tanzania.

CHAPTER VI: LIMITATION

There are several limitations to this study. First, there are similar studies conducted that included measurements of thyroid gland size. Studies like the one done by Chyan et al showed that incidence of HT, in patients with orophangeal cancer who were treated with RT to the neck decreased where the initial thyroid volume was $8cm^3$ or more [49]. In our studythyroid size measurement was not possible as there was only one radiologist on-site who could perform this test and this person was not consistently available. Thyroid iodine uptake was not possible during the study period as there was frequent stock outs of radiopharmaceutical materials. Secondary this was a small sample size and short follow up period. This study did however include more patients compared to reported studies on this similar topic. A period of nine months post radiation therapy is a short follow up period to make any inferences and conclusions.

CHAPTER IV: RECOMMENDATIONS

The results of this study help us to draw the following recommendations to all centers using cobalt 60 radiation machines with 2D planning in order to improve the care of patients receiving radiation to the supraclavicular region and head and neck in general.

- To have routine baseline measurement of thyroid gland size prior to radiation and every after 6 months on follow up post radiotherapy.
- To have routine baseline thyroid gland hormones (TSH, T4 and T3) levels measured and every 6 months on follow up post radiotherapy.
- To educate patients of the possible side effects of radiation the thyroid gland before initiating treatment and on subsequent follow up visits.
- To educate patients on the early symptoms of hypothyroidism and what to do when these are recognized.

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APPENDICES

I. Data abstraction form

Identification

File Registration number……………………………………………………

Age…………………………………………………………

Residence……………………………………………………

Disease characteristic

Disease site……………………………………………………

Disease histology……………………………………………………

Disease Grade……………………………………………………….

Hormonal status……………………………………………………….

Stage of the disease……………………………………………………

Treatment received

Chemotherapy

Types of chemotherapy regimen/protocol…………………………………………………

Number of cycles received…………………………………………………

Radiotherapy

Total dose given to the chest…………………………………………………………………

Total dose given to the supraclavicular lymph node……………………………………………

Field size used in treating the chest wall……………………………………………………

Field size used in treating supraclavicular lymph nodes………………………………………

Blocks if used …...Yes…. No……and site………size……………………………….

Surgery

MRM

Breast conserving surgery

Hormonal therapy

Tamoxifen…………………………………………………..

Letrozole…………………………………………………………………

Targeted therapy

Herceptin

Yes …………………

No……………………..

Baseline/3months/6months/12month(circle the period)

Thyroid gland function data

TSH……………..

T4……………….

T3………………

Follow up Schedule

Follow up period	Tests to be done
Base line	T3, T4, TSH,
3 months post treatment	T3, T4, TSH,
6 months post treatment	T3, T4, TSH,
12 months post treatment	T3, T4, TSH,

II. Informed consent

Research information for patient
Study Title:

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

Researcher: Fidel Rubagumya, MD

Institution: Muhimbili University of Health and Allied Sciences

Contact: Fidel Rubagumya

Email: fidel.rubagumya@yahoo.com

Daytime number: +255 (0) 788 80 5010

Afterhours: +255 (0) 788 80 5010

Sir or Madam,

We are working to assess the effects of supraclavicular lymph radiation to the thyroid gland in breast cancer patients treated at Ocean Road Cancer Institute. We hope that the information from this study will give us new knowledge on the side effect due to radiation and from this new measure will be taken to minimize thyroid gland radiation exposure.

We are inviting you to consider helping us in this research. Your participation in this research is entirely voluntary. If you do not wish to participate, this will not affect in any way the care or services that you receive from your doctors, nurses, and other healthcare workers here at Ocean Road Cancer Institute.

The study will include taking blood samples to measure the thyroid gland hormones. Allthese tests will be done before radiation, three, six and twelve months after radiation. If you agree to participate, the studyresearch assistant will enroll you, guide and direct you through the process of getting all these tests.

If at any time you would like to stop the interview or withdraw from the study, you are free to do so, and this will not affect in any way the care or services that you receive from your doctors, nurses, and other healthcare workers at the hospital.

The information obtained during this research shall be kept confidential. We will do this by keeping all data safe in locked cabinets. Also, we will take your name and your medical record number out of the information that we use to look at the study results, so that we can keep your information private. In addition, the study research assistant who speaks with you will not discuss your information with anyone else outside the research study without your permission when required.

There may be no benefit to you of participating in this research other than knowing the status of your thyroid gland especially post radiation.All the tests mentioned above have no known risks that will hinder you from participating in the study. Your name will be connected to the information you provide, so there is a small risk that someone outside of the study might learn confidential information about you. We will make this risk as small as possible by keeping all of the papers for this study in a locked cabinet. After we take the information from the paper to the computer, your name will NOT be connected with your information.

Please feel free to ask any questions to the research assistant for more information on this research. Should you wish to talk with us at any time about this consent form or for more information, you may contact Dr Fidel Rubagumya at 0788805010
Questions about your rights as a participant please contact: MUHAS IRB team

Informed consent form

I hereby confirm that I have been informed by the study interviewer about the nature, conduct, benefits and risks of the study "**Thyroid function post supraclavicular lymph node irradiation in patients with breast cancer"**

- I have read or heard and understood the above information
- I am aware that the results of the study, including personal details such as my sex, age, and diagnosis will be made anonymous (separated from my name) and then processed into a study report.
- In view of the requirements of research, I agree that the data can be processed in a computerized system by the research team or on their behalf.
- I have understood that I can, at any stage, without disadvantage to the care and services I receive, withdraw my consent and participation in the study.

PARTICIPANT:
Printed Name Signature Date and Time

Study Staff:

Name Signature Date and Time

Ridhaa

MaelezoUtafitikwamgonjwa

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

Mtafiti: Fidel Rubagumya, MD
Taasisi: Chuo Kikuu cha TibanaSayansi Muhimbili
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Ndugu,

Tunafanyakaziyakutathminiatharizinazowezakutokeakatikatezi (**thyroid gland)**baadayatibayamionzikatika (**supraclavicular lymphnode**) kwawagonjwawenyesarataniyamatitiwaliotibiwakatikataasisiyasaratani Ocean Road. Ni matumainiyetukwambataarifakutokakatikautafitihuuitatupamaarifamapyajuuyaatharizamionzina hatuahiimpyaitachukuliwailikupunguzakiasi cha mionzikatikatezi(thyroid gland) Tunakukaribishakufikiriakutusaidiakatikautafitihuu. Ushirikiwakokatikautafitihuunihiarikabisa. Kama hutapendakushiriki, hiihaitaathirikwanamnayoyoteilehudumaunazopokeakutokakwamadaktariwako, wauguzi, nawafanyakaziwenginewaafyahapakatikaTaasisiyaSarataniya Ocean Road. Utafitihuuutajumuishauchukuawasampulizadamukupimahomonizatezi(thyroid gland). Vipimavyotevitafanyikakablayamionzi, miezimitatu, sitanakuminambilibaadayamionzi. Kama umekubalikushiriki,msaidiziwautafitiatakuandikisha, kukuongozanakukuelekezakupitiamchakatowakupatavipimovyotehivi. Kama wakatiwowoteungependakuachamahojiano au kujiondoakatikautafiti,upohurukufanyahivyo, nahiihaitaathirikwanamnayoyoteilehudumaunazopokeakutokakwamadaktariwako, wauguzi, nawafanyakaziwenginewaafyakatikaHospitali.

Taarifazitakazopatikanawakatiwautafitihuuzitakuwasiri.

Tutafanyahivyokwakuwekataarifazotekwausalamakatikakabatizilizofungwa.

Pia,tutachukuajinalakonanambayarekodiyamatibabuyakonjeyataarifaambazotutangaliakatikamatokeoyautafiti, ilituwezekuwekataarifazakobinafsi.

Aidha,mtafitimsaidiziatakayeongeanawewehatajadilitaarifazakonamtumwingineyeyotenjeyautafitibilaidhiniyakowakatiikihitajika.

Kunawezakusiwenafaidayawewekushirikikatikautafitihuuzaidiyakujuahaliyateziyakohasabaadayakupatamionzi.

Vipimovyotevilivyotajwahapojuuhavinahatariinayojulikanaambayoitakuzuiakushirikikatikautafiti. Jinalakolitaambatananataarifautakazotoa, hivyokunahatarindogokwambamtualiyenjeyautafitianawezakujifunzataarifazasirikuhusuwewe.

Tutafanyahatarihiikuandogoiwezekanavyokwakuhifadhikaratasizotezautafitihuukatikakabatiiliyofungwa. Baadayakuchukuataarifakutokakwenyekaratasinakuwekakwenyekompyuta, jinalakohalitaambatanishwanataarifazako.

Tafadhalijisikiehurukuulizamaswaliyoyotekwamtafitimsaidizikwahabarizaidijuuyautafitihuu.

Kama utapendakuzungumzanasisiwakatiwowotekuhusuhiifomuyaridhaa au kwataarifazaidi, unawezakuwasilianana Dr Fidel Rubagumyakatika 0788805010

Maswalikuhusuhakizakokamamshirikitafadhaliwasilianana: MUHAS IRB timu

Fomuyaridhaa

Ninathibitishakwambanimefahamishwanamtafitikuhusuasili, mwenendo, faidanahatariyautafiti "**Thyroid function post supraclavicular lymph node irradiation I patients with breast cancer**"

• Nimesoma au kusikianakuelewataarifazilizopohapojuu

• Ninatambuakuwamatokeoyautafiti, ikiwanipamojanataarifazabinafsikama vile jinsia, umri, nautambuzizitafanywabilamajina (kutengwanajinalangu) nakishakuwekwakatikaripotiyautafiti.

• Kwamtazamowamahitajiyautafiti, nakubalikwambataarifazinawezakuwekwakatikamfumowakompyutanatimuyautafiti au kwaniabayao.

• Nimeelewakwambaninaweza, katikahatuayoyote, kuondoaridhaayakushirikikatikautafitibilamabadilikoyahudumaninazopokeapokea.

MSHIRIKI:

JinaSahihiTarehena Muda

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Mtafiti:

JinaSahihiTarehena Muda

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