RESEARCH ARTICLE

Thyroid Function after Postoperative Radiation Therapy in Patients with Breast Cancer

Edyta Wolny-Rokicka[1,2]*, Andrzej Tukiendorf[3], Jerzy Wydmański[4], Danuta Roszkowska[5], Bogusław Staniul[6], Agnieszka Zembroń-Łacny[2]

Abstract

Objective: The aim of this study was to assess thyroid function in breast cancer patients exposed to therapeutic external beam radiation. The focus was on possible progressive changes and any relationships between the incidence of primary hypothyroidism, the time required to become hypothyroid, and factors such as chemotherapy, hormonotherapy and immunotherapy. **Materials and Methods:** Seventy females undergoing 3D conformal and IMRT radiation therapy for breast cancers were enrolled in a non-randomized prospective study. The patients was divided into two groups: those after mastectomy or breast conserving surgery (BCS) were irradiated to a scar of the chest wall/breast and the ipsilateral supraclavicular and the axillary areas (supraclavicular radiotherapy group - SC-RT group – 32 patients) and the control group receiving adjuvant chest wall/breast RT only (BCT group - 38 patients).The total doses were 50.0 to 70 Gy in 5 to 7 weeks. The median follow-up term was 24 months (range, 1–40 months). Thyroid function was evaluated by measuring thyroid stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) levels. The minimum, maximum and mean thyroid gland doses for 20 Gy (V20) were calculated for all patients. **Results:** Statistically significant results were obtained for the SC-RT group. Two yearsa fter the end of RT the chance of an event was increased in 6% of the population (p=0.009) in the SC-RT group. In the BCT group no significance was noted. No statistically significant differences were found for V20, chemio-, immunotherapy and hormonotherapy or Ki67 values (p=0.12). No significant results were obtained for development of hypothyroidism and clinical factors (age, thyroid volume, treatment modalities). **Conclusion:** Radiotherapy is associated with a higher incidence of thyroid toxicity in breast cancer patients. Routine thyroid function monitoring should be recommended in such cases.

Keywords: Thyroid disorders- external beam radiation- breast cancer- hypothyroidism

Asian Pac J Cancer Prev, **17 (10)**, 4577-4581

Introduction

The relationship between breast cancer and thyroid function has been discussed from different viewpoints ever since Beatson in 1896 noticed necessity to treat thyroid gland in advanced breast cancer (Beatson 1896). Many studies showed that thyroid diseases are common among women with breast cancer (Rasmusson et al.,1987; Shering et al.,1996).

Women with breast cancer were considered to have an increased frequency of hypothyroidism - usually subclinical (Mittra et al.,1974).

Hellevik et al. reported that low levels of fT4 and high levels of TSH were associated with the increased risk of BC (Hellevik et al., 2009) . However, another study found no association between TSH levels and breast cancer risk (Kuijpens et al., 2005).

Hypothyroidism is a well-known consequence of external-beam radiotherapy to the neck encompassing a part or the whole of the thyroid gland. TSH levels are important for diagnosing subclinical diseases. Subclinical hypothyroidism is a common endocrine disorder characterized by increased levels of TSH with normal serum levels of fT4 and fT3 (Biondi et al., 2008).

The hypothyroidism has a significant impact on the deterioration of the quality of life. The primary hypothyroidism is the most common clinical late-effect of the thyroid gland irradiation in patients exposed to therapeutic doses (30.0-70.0 Gy) to the cervical region (Turner et al., 1995). Radiation-induced hypothyroidism is a frequent late effect after definitive radiotherapy in the neck area (Feen Ronjom M. 2016).Tunio et al. shows a

*[1]Department of Radiotherapy, Regional Clinical Hospital in Zielona Gora Zyty 26, 65-001 Zielona Gora, [2]University of Zielona Gora, Faculty of Medicine and Health Sciences, [3]Department of Epidemiology and Silesia Cancer Registry, [4]Department of Radiotherapy, Center of Oncology, Maria Sklodowska-Curie Memorial Institute, Branch in Gliwice, ul Wybrzeża Armii Krajowej 15,44-101 Gliwice, [5]Department of Physics, Regional Clinical Hospital in Zielona Gora Zyty 26, 65-001 Zielona Gora, [6]Department of Surgery, Regional Hospital in Sulechow, Zwyciestwa 1, 66-100 Sulechow, Poland. *For Correspondence: edyta.wolny@gmail.com*

dependency of dose-volume of irradiated thyroid gland and its influence on hypothyroidism (Tunio et al. 2015). Similar conclusions were considered at few another studes (Johansen et al. 2011 and Laway et al, 2012). The incidence of radiation-induced hypothyroidism varies considerably, however the tolerance level of the thyroid gland is poorly defined.

In this prospective but non-randomized study, we have tried to evaluate the response of the thyroid gland to radiation by assessing thyroid function among breast cancer patients before irradiation and at regular intervals thereafter.

Materials and Methods

Patient characteristics

This non-randomized, prospective study analyses of 70.0 women with breast cancer treated with radiotherapy in the Radiotherapy Department in Regional Clinical Hospital in Zielona Gora between April 2012 and May 2015. The study was conducted by one physician for a period of 2 years in which thyroid function was assessed in 38.0 women who received radiotherapy to the breast after breast conserving surgery (BCS) procedure or mastectomy – (BCT group) and in 32 women who underwent irradiation of regional lymph nodes and breast or scar – (SC-RT group). In each case, a part of the thyroid gland has been irradiated. It was documented using contouring the thyroid gland for all patients, both for patients after BCT and after mastectomy by one physician. Each treatment plan consisted of dose volume histograms (DVHs) in which was described distribution of isodoses in the critical organs and additional was shown distribution of isodoses in thyroid gland for both group.

The blood samples were drawn before radiotherapy and evaluated by measuring the serum thyroid stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) levels. None of the women were on thyroid substitution therapy. The thyroid function both of the TSH, fT3 and fT4 levels were monitored in patients every 2 or 3 months after the completion of radiation therapy for the 6 months, and then on average every 3 months. We analysed diffrent risk factors such age, treatment (radiotherapy, chemotherapy, hormonotherapy, immunotherapy) and duration of the follow-up.

Serum TSH,T3 and T4 levels were measured by electro-chemiluminescence immunoassay method using commercial kits. The reference values in our hospital for this parameters are: TSH - normal range: 0.3 - 4.2 mIU/ml, fT4 normal range: 0.9 - 1.7ng /dl and fT3 normal range: 2.0 - 4.4 pg/ml. Although hypothyroidism can be divided into clinical and subclinical classifications, we defined hypothyroidism as a TSH value greater than the maximum value of laboratory range, regardless of symptoms. None of the 70.0 women in our study had ever undergone thyroid surgery.

Radiotherapy

Three-dimensional conformal radiotherapy (3D-CRT) treatment plans were available for 67 patients. Intensity-modulated radiotherapy (IMRT) treatment plans were available for 3 women.

All targets and thyroid glands were contoured manually on computed tomography (CT) scan. CT slice thickness was 0.3- 0.5 cm.

The total volume of thyroid gland, minimum, maximum and mean thyroid dose of the thyroid gland and persentage of thyroid gland volume absorbing 20 Gy (V20) were calculated from the dose–volume histograms (DVHs) based on the radiotherapy planning system (RTPS) XiO-release v4.60.00.4 CMS software the ELECTA group.

Statistical Analysis

In the study, a mixed effects logistic regression was used to model a binary outcome variable (i.e. clinical and subclinical events). The statistically significant results were obtained for the SC-RT group only while for BCT group the regression modeling was intractable. Based on the estimated parameters the odds ratio was expressed for the time since RT: OR=1.003(1.001-1.005) and a logistic curve was plotted to model a probability of the event in patients (Figure 1). It can be seen in Figure 1 that after two years since RT, the predicted chance of the event in the analyzed SC-RT group of patients increased up to 6%.

Results

Clinical characteristics of patients are presented in Table 1. In 70.0 breast cancer patient, median follow-up time in BCT group was 325.0 days and 400.0 days in SC-RT group, respectively. Median age was 58.0 years for BCT group and 55.5 years for SC-RT group. All patients underwent surgical treatment (60% with breast conserving surgery, 40% with mastectomy) and followed by radiotherapy. A 6-MV photon beam was used for all patients with fractionation from 2 Gy to 2.5 Gy per fraction. The total of 32 patients received treatment with 50 Gy which the target volume included the breast (after BCS) or the chest wall (after mastectomy), the ipsilateral supra-and infraclavicular fossa, ipsilateral lymph nodes along the internal mammary artery and ipsilateral axilla. 38 patients received 50 Gy irradiation to the whole-breast (WBI) and 10 to 20 Gy as a boost to a tumor bed after BCS. Estrogen receptor was positive in 95% of the population in BCT group and 63 % in SC-RT group. Progesterone receptor was positive in BCT group and SC-RT group - 87% and 72% respectively. Mean of Ki67

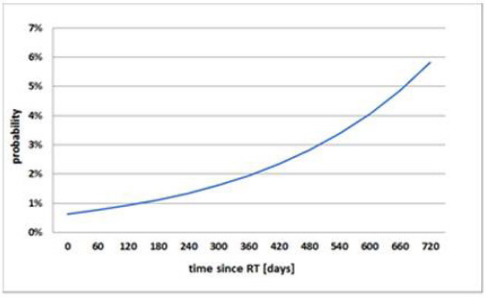

Figure 1. Probability of the Event in Patients vs. Days Since RT

Table 1. Patient and Clinical Tumor Characteristics in 70.0 Patients

Characteristics	BCT group 1- (38-100%)	Supraclavicular RT group (32-100%)
Age		
Median	58	55.5
70-79	5 (13)	2 (6)
61-69	14 (37)	8(25)
<60	19 (50)	22 (69)
ECOG performance status		
0	18 (47)	12 (38)
1	19 (50)	20 (62)
2	1 (3)	
Histology		
Ductal	8 (21)	16 (50)
Lobular	3 (8)	4 (12)
NST	27 (71)	12 (38)
ER status		
Positive	36 (95)	20 (63)
Negative	2 (5)	12 (37)
PR status		
Positive	33 (87)	23(72)
Negative	5 (13)	9 (28)
Treatment		
Chemotherapy + Immuntherapy	2 (5)	8 (25)
Chemotherapy + Hormonotherapy	0	23 (72)
Hormonotherapy	36 (95)	1 (3)
Breast conserving surgery	38 (100)	4 (12)
Mastectomy	0	28 (88)

ECOG, Eastern Cooperative Oncology Group; NST, Non Specific Type; ER, Estrogen Receptor; PR, Progesterone Receptor; BCT, Breast Conserving Therapy; RT, Radiation Therapy

for BCT group was 16.5 (0.0 -70.0) and 5.8 (4.0 – 80.0) for SC-RT group. The mean values of parameters of the thyroid gland before and after treatment are shown in Table 2 for the both groups. The mean volume of the thyroid gland before radiation therapy was 1.4 (0.4- 4.9) cm^3 in BCT group and 1.6 (0.2- 6.9) cm3 in SC-RT group. Our results showed that only radiotherapy was associated with a higher incidence of thyroid toxicity. We noticed

Table 2. Characteristics of Parameters of the Thyroid Gland for Two Groups

	BCT Group	SC-RT Group
Volume (range) cm^3	1.4 (0.4-4.9)	1.6(0.2-6.9)
	Before Radiotherapy	
TSH Mean (SD range)	1.4 (±0.9)	1.6 (±1.4)
fT3 Mean (SD range)	2.9 (±0.4)	3.3 (± 0.7)
fT4 Mean (SD range)	1.1 (±0.2)	1.2 (± 0.3)
	After Radiotherapy	
TSH Mean (SD range)	1.7 (±1.1)	2.2 (±1.8)
fT3 Mean (SD range)	3.1 (±0.5)	3.2 (±0.6)
fT4 Mean (SD range)	1.1 (±0.3)	1.2 (±0.3)
V20 Mean (SD range)	0.0	41.0 (±17.1)
V20 Median	0.0	44.1
Median dose	20.0 cGy	1957.5 cGy
Mean dose (SD range)	20.4 cGy (±10.5)	1934 cGy (±974.5)

normal range for parameters, TSH, (thyroid stimulating hormone) - 0.3 - 4.2 mIU/ml; fT3, (free triiodothyronine) - 2.0 - 4.4 pg/ml; fT4, (free thyroxine) - 0.93 - 1.7ng /dl; BCT, Breast Conserving Therapy; SC-RT, Supraclavicular Radiotherapy; SD,Standard Deviation; V20, dose -volume of distribution 20Gy; cGy, centigray[SI unit][3]

that after two years since the radiotherapy the adverse event occurred in 6 % of the population (p=0.009) in SC-RT group. In BCT group it was not significant. No statistically significant differences was found for V20, chemio-, imminotherapy and hormonotherapy or Ki67 (p=0,12). No significant results were obtained between the development of hypothyroidism and clinical factors (age, thyroid volume, treatment modalities such as: hormonotherapy, neoadjuvant/adjuvant chemotherapy and immunotherapy).

Discussion

In our study, the incidence of RT-induced hypothyroidism was exposed after two years since the radiotherapy in 6% population in BC patients receiving SC-RT.

This result of hypothyroidism is connected with literature and it is one of the late side effects after the neck RT, which includes the whole or a part the thyroid glands (Glatstein et al., 1971; Alterio et al., 2007; Chougule et al., 2011; Mi Young et al., 2014; Bernat et al., 2014) This complication after mantle irradiation in Hodgkin's disease is well documented (Fuks et al.,1976; Schimpff et al., 1980). Thyroid dysfunction develops slowly - up to 15% of patients showing dysfunction and maximum of 66% reached at about 6 year (Schimpff et al., 1980). In a study by Laway et al., TSH increased significantly after 3 months in patients who had received radiotherapy to the neck (Laway et al., 2012). Glatstein et al. also observed high TSH within 1 year (Glatstein et al., 1971; Murthy et al., 2012). Tamura et al.showed that the incidence of high TSH increased from 26% after 2 years to 62% after 6-12 years (Tamura et al., 1981). Two kinds of radiation as described above, which induce thyroid damage, are: subacute damage and late damage. A late damage may have a different mechanism than a subacute. A radiation as a risk factor for the development of hypothyroidism remains controversial. Hypothyroidism is associated with damage of small thyroid vessels and artheriosclerosis of larger vessels and additionally contribute to mechanisms of parenchymal injury of thyroid cells and secondary capsular fibrosis (Jereczek-Fossa et al., 2004). Kuten et al. showed a 40% risk of hypothyroidism in patients with a head and neck cancer irradiated with 30-45 Gy and up to 27% for those receiving less - patients with Hodgkin's disease (Kuten et al., 1996). Emami et al.suggested a tolerance dose of 45 Gy, which leads to development of clinical hypothyroidism in 8% within 5 years after radiotherapy with 45 Gy (Emami et al., 1991). According to Yoden et al. V30 Gy had a significant impact on the peak level of TSH (Yoden et al., 2001; Fujiwara et al., 2015). The same study showed that the percentage volume of the thyroid gland receiving doses between 10-60 Gy (V10-V60) can act as a predictor of hypothyroidism. Many clinicians often underestimate the importance of hypothyroidism. The authors such as Cristofanili at al. indicated that primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma (61%) - more indolent disease (Cristofanili et al., 2005). This protective role may be assiciated with iodide and its antioxidant effect as well as biologic influence of T3 at the cellular level through a direct interaction with the thyroid receptor (Venturi et al., 2000; Kilbane et al., 2000). There is a question of secondary hypothyroidism after radiotherapy. Does it have any influence on patients after treatment, their follow-up and incidence of metastasis? This results cannot be easily extrapolated to all breast cancer patients. Our study assessed breast cancer patients who had received radiotherapy to the neck encompassing a part of the thyroid gland. We detected the incidence of hypothyroidism in 6% of patients after 2 years after radiotherapy in comparison to the patients who did not have irradiation to the neck region (p=0.009). These findings are almost identical to the study of Laway BA et al. - 10% (Laway et al., 2012). One of the previous studies suggested no association between radiation and development of hypothyroidism in breast cancer patients (Huang et al., 2001). Other investigators suggested that chemotherapy and hormonal therapy could have additional modifying effects (Bruning et al., 1985; Koc et al., 2001). Bruning et al reported that postoperative irradiation of supraclavicular lymph nodes in postmenopausal breast cancer patients may frequently lead to subclinical thyroid dysfunction (Bruning et al., 1985). Tunio et al. in pilot study found that patients with V30 ≥50% and small glandular volumes are at high risk to develop RT-induced hypothyroidism (Tunio et al., 2015). However, all patients, regardless of RT status, were more likely to be diagnosed with hypothyroidism compared with cancer-free controls (HR 5 1.2; 95% CI, 1.2–1.2) (Smith et al.,2008). National Comprehensive Cancer Network guidelines recommendation routine screening of thyroid function at least annually after radiation therapy in Hodgkin disease and head and neck cancer patients if irradiated to the neck (NCCN version 1,2; 2015).

The survival of breast cancer patients is increasing, therefore the incidence of radiation-induced hypothyroidism may be an important factor of the late toxicity. A routine thyroid function monitoring in all breast cancer patients after radiotherapy should be consider. Limitation of our study are the small sample size and high heterogeneity.

References

Alterio D, Jereczek-Fossa BA, Franchi B, et al (2007). Thyroid disorders in patients treated with radiotherapy for head-and-neck cancer: a retrospective analysis of seventy-three patients. *Int J Radiat Oncol Biol Phys*, **67**, 144-50.

Beatson GT (1896). On the treatment of inoperable cases of carcinoma of the mama: Suggestions for a new method of treatment, with illustrative cases. *Lancet,* **148**, 162-65.

Bernat L, Hrusak D (2014).Hypothyroidism after radiotherapy of head and neck cancer. *J Craniomaxillofac Surg*, **42**, 356-61.

Biondi B, Cooper DS (2008). The clinical significance of subclinical thyroid dysfunction. *Endocr Rev*, **29**, 76-131.

Bruning P, Bonfrer J, De Jong-Bakker M, Nooyen W, Burgers M (1985). Primary hypothyroidism in breast cancer patients with irradiated supraclavicular lymph nodes. *Br J Cancer*, **51**,659-63.

Chougule A, Kochar B (2011). Thyroid dysfunction following therapeutic external radiation to head and neck cancer. *Asian Pac J Cancer Prev*, **12**, 443-5.

Cristofanilli M, Yamamura Y, Kau S-W, et al (2005). Thyroid Hormone and Breast Carcinoma. *Cancer*, **103**, 1122-8.

Emami B, Lyman J, Brown A, et al (1991). Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*, **21**,109-22.

Feen Ronjom M. (2016). Radiation-induced hypothyroidism after treatment of head and neck cancer. *Dan Med J*, **63**, B5213

Fuks Z, Glatsteien E, Marsa GW, Bagshaw MA, Kaplan HS (1976). Long-term effects of external radiation on the pituitary and thyroid glands. *Cancer*, **37**, 1152.

Fujiwara M, Kamikonya N, Odawara S et al (2015). The threshold of hypothyroidism after radiation therapy for head and neck cancer: a retrospective analysis of 116 cases. *J Radiat Res*, **56**, 577-82.

Glatstein E, McHardy-Young S, Brast N, Eltringham JR, Kriss JP (1971). Alterations in serum thyrotropin (TSH) and thyroid function following radiotherapy in patients with malignant lymphoma. *J Clin Endocrinol Metab*, **32**, 833-41.

Hellevik AI, Asvold BO, Bjoro T, (2009).Thyroid function and cancer risk: a prospective population study. *Cancer Epidemiol Biomarkers Prev*, **18**, 570-4.

Huang J, Walker R, Groome PG, Shelley W, Mackillop WJ (2001). Risk of thyroid carcinoma in a female population after radiotherapy for breast carcinoma. *Cancer*, **92**, 1411-18.

Jereczek-Fossa BA, Alterio D, Jassem J, et al (2004). Radiotherapy-induced thyroid disorders. Cancer Treat Rev, 30, 369–84 Johansen S, Reinertsen KV, Knutstad K, Olsen DR, Fossa SD (2011). Dose distribution in the thyroid gland following radiation therapy of breast cancer – A retrospective study. *Radiat Oncol*, **6**, 68.

Kilbane MT, Ajjan RA, Weetman AP, et al (2000). Tissue iodine content and serum-mediated 125I uptake-blocking activity in breast cancer. *J Clin Endocrinol Metab*, **3**,1245-50.

Koc M, Capoglu I, Unuvar N (2001). Does the tamoxifen increase thyroid dysfunction after loco-regional irradiation of breast cancer? *Radiother Oncol*, **59**, 361-62.

Kuijpens JL, Nyklictek I, Louwman MW, et al (2005). Hypothyroidism might be related to breast cancer in post-menopausal women. *Thyroid*, **15**, 1253-9.

Kuten A, Lubochitski R, Fishman G, Dale J, Stein ME (1996). Postradiotherapy hypothyroidism; Radiation dose response and chemotherapeutic radiosensitization at less than 40Gy. *J Surg Oncol*, **61**, 281-83.

Laway BA, Shafi KM, Majid S, et al (2012).Incidence of primary hypothyroidism in patients exposed to therapeutic external beam radiation, where radiation portals include a part or whole of the thyroid gland. *Indian J of Endocrinol Metab*, **16**, 329-31.

Rasmusson B, Rasmussen UF, Hegedus L, et al (1987). Thyroid function in patients with breast cancer. *J Cancer Clin Oncol*, **23**, 553-56.

Mittra I, Hayward JL (1974).Hypothalamic-pituitary-thyroid axis in breast cancer. *Lancet, 1*, 885-89.

Mi Young Kim, Tosol Yu, Hong-Gyun Wu (2014). Dose-volumetric parameters for predicting hypothyroidism after radiotherapy for head and neck cancer. *Jpn J Clin Oncol*, **44**, 331-37.

Murthy V, Narang K, Ghosh-Laskar S, et al (2014). Hypothyroidism after 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy for head and neck cancers: prospective data from 2 randomized controlled trials. *Head Neck*, **36**, 1573-80.

National Comprehemsive Cancer Network (2015). Availableat:http://www.nccn.org/ Accessed version 1.2015 et 2.2015.

Schimpff SC, Diggs CH, Wiswell JG, Salvatore PC,Wiernik PH (1980). Radiation-related thyroid dysfunction. Implications for the treatment of Hodgkin's disease. *Ann Intern Med*, **92**, 91-8.

Shering SG, Zbar AP, Moriatry M (1996).Thyroid disorders and breast cancer. *Eur J Cancer Prev*, *5*, 504-6.

Smith GL, Smith BD, Giordano SH, et al (2008). Risk of hypothyroidism in older breast cancer patients treated with radiation. *Cancer*, **112**,1371-9.

Tamura K, Shimaoka K, Friedman M (1981). Thyroid abnormalities associated with treatment of malignant lymphoma. Cancer, **47**, 2704-11.

Tunio MA, Al Asiri M, Bayoumi Y, et al (2015). Is thyroid gland an organ at risk in breast cancer patients treated with locoregional radiotherapy? Results of a pilot study. *J Can Res Ther*, **11**, 684-9.

Turner SL, Tiver KW, Boyages SC (1995). Thyroid dysfunction following radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys*, **31**, 279-83.

Venturi S, Donati FM, Venturi A, et al (2000). Role of iodine in evolution and carcinogenesis of thyroid, breast and stomach. *Adv Clin Pathol*, **4,** 11–17.

Yoden E, Maruta T, Soejima T, et al (2001). Hypothyroidism after radiotherapy to the neck. *Int J Radiat Oncol Biol Phys*, **51**, 337-38.