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A Comparison of Thyroid Dose Distribution in 3-D Conformal Radiotherapy and Tomotherapy in Patients with Breast Cancer

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Abstract

Background and purpose: During the radiotherapy of breast cancer, especially when the supraclavicular lymph nodes are planned to be treated, a portion of thyroid gland may also be included in the treatment field. In this study we compared thyroid gland dose volume histograms (DVHs) of breast cancer patients receiving radiotherapy, planned in both CT-based three-dimensional planning system and MVCT-based image guidance aspect of helical tomotherapy system.

Material and method: 20 breast carcinoma patients who were treated with 3-D conformal radiotherapy technique were evaluated concerning their thyroid gland dose distribution. The estimated minimum, mean and maximum thyroid gland doses were calculated for both 3-D conformal radiothreapy and tomothreapy planning systems. Additionally the volume of thyroid gland that received less than 30 Gy and more than 30 Gy were determined.

Results: The maximum, mean and minimum doses of thyroid glands supposed to receive were found to be better with tomotherapy comparing to 3-D conformal therapy plans. The thyroid gland volume that receives more than 30 Gy was smaller in tomothreapy planning system comparing to 3-D conformal therapy planning system.

Conclusion: Lower doses of radiation exposure to thyroid gland is possible with Tomotherapy.

Keywords: Breast cancer; Thyroid; Radiotherapy; Dose distribution

Introduction

During the radiotherapy of breast cancer, especially when the supraclavicular lymph nodes are planned to be treated, a portion of thyroid gland may also be included in the treatment field. Although the evidence of hypothyroidism secondary to external neck radiation in Hodgkin disease and head-neck cancer patients is well established [1,2] there are only a few studies in the literature investigating the association between hypothyroidism and radiotherapy in patients with breast cancer [3-7]. The incidence of hypothyroidism may reach up to 30-50% 5 years or more after radiotherapy in patients with Hodgkin disease and head-neck cancers [8]. In such patients, the whole thyroid gland is usually located within the radiation fields. Less is known about the thyroid function in patients with breast cancer who receives locoregional radiotherapy and thyroid gland is partially involved in supraclavicular region. An important determinant of hypothyroidism is total volume of the thyroid tissue. In supraclavicular field radiotherapy even if a part of the thyroid gland is included to the radiotherapy field the development of hypothyroidism is a possibility in patients with small total thyroid gland volume. Johansen et al. reported that over the doses of 30 Gy the patients with small thyroid glands are at particular risk to develop hypothyroidism Bonato et al. [9] confirmed in their study that hypothyroid individuals had smaller glands than those with normally functioning glands [4]. Since thyroid gland volume varies from patient to patient, the dose that the thyroid gland received must be kept below 30 Gy in planning supraclavicular field radiotherapy. Reinertsen et al. [4] reported that the prevalence of hypothyroidism is 18% in breast cancer patients as compared to 6% prevalence of hypothyroidism in general population in Norway [3]. During recent years, many RT centers have changed their practice from using standardized field arrangements such as 3-D conformal radiotherapy and IG-IMRT. In limited number of studies in the literature it was shown that the radiation dose received by the thyroid tissue was higher in patients with breast carcinoma treated with 3-D conformal radiotherapy and IMRT techniques comparing to patients treated with 2-D radiotherapy techniques. In this study we compared thyroid gland dose volume histograms (DVHs) of breast cancer patients receiving radiotherapy, planned in both CT-based three-dimensional planning system and MVCT-based image guidance aspect of helical tomotherapy system.

Material and Methods

In this study 20 breast carcinoma patients who were treated with 3-D conformal radiotherapy technique and received radiotherapy to their supraclavicular fossa and breast/chess wall were evaluated concerning their thyroid gland dose distribution. The patients had Stage II/III breast cancer and had either modified radical mastectomy or breast conserving surgery with axillary lymph node dissection for their surgical treatment. The mean age of the patients was 51 (38-80) and they had no known thyroid disease. All patients received 3-D conformal radiotherapy and we carried out tomotherapy treatment planning at the same time and compared the data from 3-D conformal radiotherapy and tomotherapy planning systems. The virtual simulation of the patients was carried out in accordance with our standard protocol. According to this protocol the patients were

positioned supine on a breast board with the ipsilateral arm extended above the head and the head turned to the controlateral side. A non-contrast CT scan was obtained to 3 mm slice and CT scans were then transferred to Tomocon. Workstation for definition of target volumes and critical structures especially thyroid gland. For 3-D conformal tangent technique treatment plans, PresicePlan Release 2.16-28.76 (Electa Crawley, UK) was used. All patients were treated with 4-field RT in which the target volume included the breast or chest wall, ipsilateral axilla and supraclavicular fossa. It was assured that the breast/chest wall and supraclavicular fossa received a total dose of 50 Gy. Four of the patients received an additional boost of 10 Gy to the tumor bed. Tomotherapy plans were completed in the Hi-Art II planning system (TomoTherapy Inc, Madison, WI).In tomotherapy planning systems 3 major factors are defined :the field width, the pitch and the modulation factor. The longitudinal field width is described as the fan beam (http://en.wikipedia.org/wiki/Fan-beam_antenna) width. The pitch is the ratio of the field with for every gantry rotation and table movements. The modulation factor is described as the ratio of the mean intensity of all bundles to the intensity of the most intense bundle. In our study the field width, the pitch and the modulation factor were 5.02, 0.287 and 2 respectively. The tomothreapy plans were done so that breast/chest wall and supraclavicular fossa should receive a total dose 50 Gy in 25 fractions. Four of the patients were planned as if to receive an additional boost of 10 Gy to the tumor bed. In both plans 95% (47, 5 Gy) and 107% (53, 5 Gy) of PTV were evaluated. (V 95%-V 107%). In both 3-D conformal radiotherapy and tomotherapy plans required target volume coverage were assured and thyroid gland dose distributions were evaluated after proper dose constrains to the organ at risk (e.g. heart, lung, contralateral breast) were applied. For the purpose of the current study the individual volume of the thyroid gland was calculated. The estimated minimum, mean and maximum thyroid gland doses were calculated for both of the planning systems. Additionally the volume of thyroid gland that received less than 30 Gy and more than 30 Gy were determined. (V<30 Gy and V>30 Gy).

Results

Table 1 shows the estimated minimum, mean and maximum thyroid gland doses and the volume of thyroid gland that received less than 30 Gy and more than 30 Gy in both Precise planning system and tomothreapy planning system .It also gives p values comparing these two planning systems .The maximum, mean and minimum doses of thyroid glands supposed to receive were found to be better comparing to 3-D conformal therapy plans. These differences were statistically significant (p<0,001). The thyroid gland volume that receives more than 30 Gy was smaller whereas the thyroid gland volume that receives less than 30 Gy was greater in tomothreapy planning system comparing to 3-D conformal therapy planning system. (p<0,001) (Figure 1). The dose distributions of the organs at risk (e.g. heart, lung, contralateral breast) were given in Table 2 and Figure 2. For statistical analysis Student's paired t test and Wilcoxon's tests were used.

	3-D Conformal RT	Tomotherapy	P value
Minimum dose (Gy)	2.51 ± 1.14	6.85 ± 1.83	p<0.001
Maximum dose (Gy)	55.08 ± 2.75	52.62 ± 0.67	p<0.001
Mean dose (Gy)	28.83 ± 3.75	19.59 ± 6.84	p<0.001
< 30 Gy volum (%)	49.4 ± 7.4	59.3 ± 8.0	p<0.001
> 30 Gy volume (%)	50.5 ± 7.4	40.6 ± 8.0	p<0.001

Table 1: Thyroid dose distribution. Data: mean ± standart deviation

		3-D Conformal RT	Tomotherapy	P value
Heart	V5 %	21	99	<0.001
	V30 %	8	11	>0.05
Lung	V5 %	36	97	<0.001
	V20 %	18	16	>0.05
Contralateral Breast	Gy	1.2	6.2	<0.001

Table 2: The dose distributions in organ at risc.

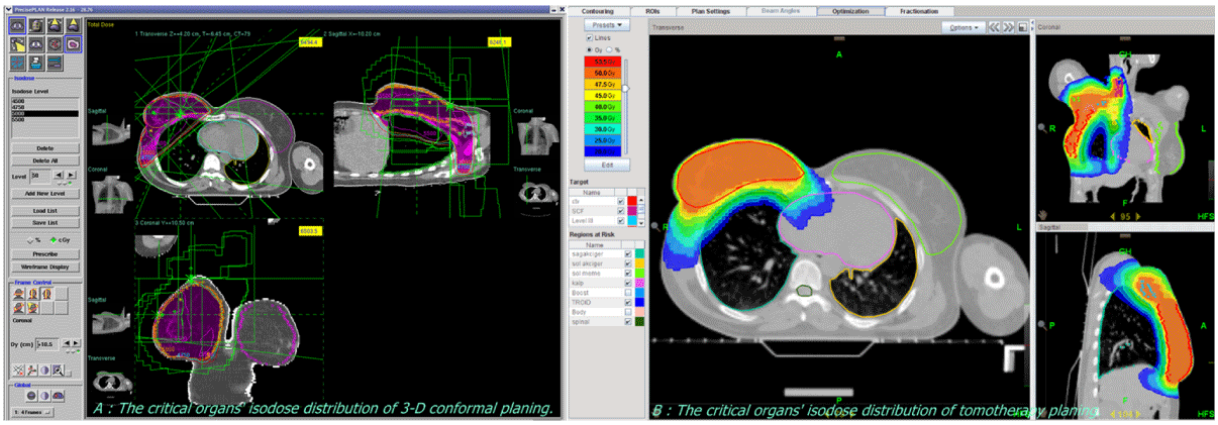

Figure 1: The illustrations of estimated dose distributions of thyroid gland.

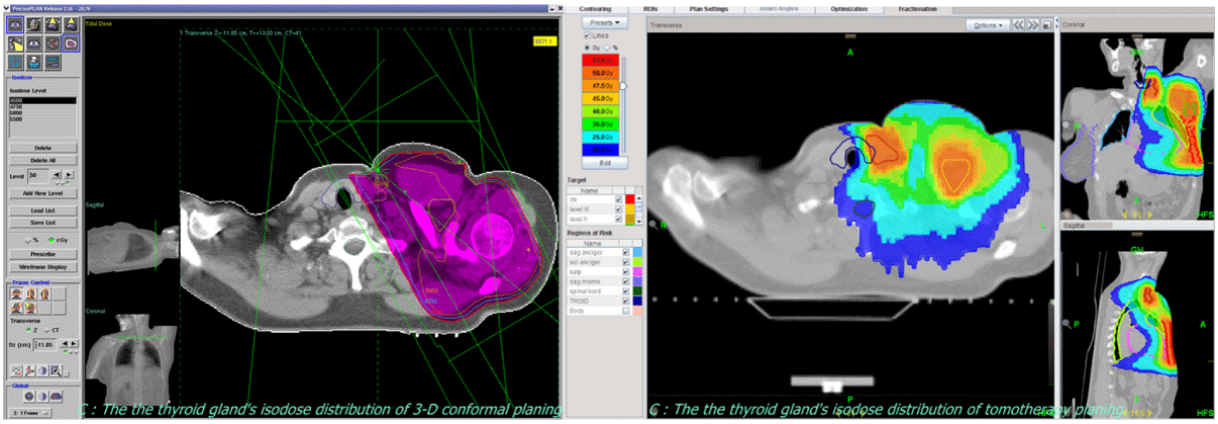

Figure 2: The illustrations of estimated dose distributions of organs at risc.

Discussion

In the literature the threshold value of radiation received by thyroid during breast cancer treatment causing hypothyroidism is not clear. For this reason during radiotherapy planning for breast carcinoma, thyroid DVH and thyroid function tests should be evaluated routinely It is essential to monitor complications of cancer treatment in the follow up procedure for all cancer survival [10]. During head and neck cancer radiotherapy, radiation induced hypothyroidism is a well-known side effect. Considering the continuing risk of hypothyroidism in these patients, a life-long TSH testing is warranted. Studies carried out in head and neck cancer patients have helped to learn the pathophysiology that underlies the development of hypothyroidism. Not only parancymal thyroid cell injury but also radiation induced damage to small thyroid vessels and atherosclerosis of large vessels contribute hypothyroidism formation. Lastly evidences suggest that immune mediated damage may further play a role in outcome [11]. The radiation dose is an important factor for thyroid dysfunction [12,13]. Tell et al. reported that the volume of thyroid irradiated is important for development of radiation induced hypothyroidism however they could not find that a higher RT dose to the primary site had a significant correlation with the risk of developing hypothyroidism. During radiotherapy for breast cancer, although unilateral lobe of the thyroid remains in the radiotherapy area and therefore it is assumed that the incidence of hypothyroidism would be lower; Johansen et al [9] reported that the subvolume receiving ≥ 30 Gy seems to determine whether or not sufficient thyroxin is produced after radiotherapy [9]. Yoden et al. [14] have suggested that a predictor of hypothyroidism is the percentage volume of the thyroid gland receiving doses between10-60 Gy According to Yoden et al. V30 Gy had a significant impact on the peak level of TSH [14]. Sigurdson et al. [15] studied risk of thyroid cancer in a large group of patients treated for childhood cancer and found convincing evidence for a nonlinear dose response at thyroid doses exceeding 30 Gy [15]. The time course of developing late thyroid effects is highly variable. The more risky period for development of hypothyroidism is 3-5 years since the diagnosis whereas the risk for nodules increased ≥ 10 years from diagnosis [16]. For this reason the thyroid functions needs to be followed more than 10 years in patients with breast carcinoma who received supraclavicular radiotherapy. The findings in this follow up needs to be compared with DVHs of thyroid. We need a consensus on a guideline for thyroid disease follow up in breast cancer patients just as we have in head and neck cancers. Another topic of discussion is why normal tissues exposed to radiation continue to function for several years after irradiation and then progressively lose their function. In the case of 131I therapy for hyperthyroidism, hypothyroidism may develop within the first months after such therapy or in subsequent years [17,18]. The acute effect may be the result of directly carried radioactivity to thyroid cells with 131I.Another mechanism related with Iodine may be important for development of hypothyroidism in breast cancer. Giani et al. [19] reported a higher frequency of thyroid disease in patients with breast neoplasia [19]. Mammary gland epithelium and thyroid epithelial cells share a property of concentrating iodine by a membrane active transport mechanism [20,21]. The question to what extent this accounts for the relationship between iodine deficiency and breast disease is unclear. Tell et al found that a high TSH value before RT, that may indicate autoimmune thyroid disease, is a significant factor for the development of hypothyroidism. They suggested not only thyroid hormones, but also thyroid autoantibodies should be included in the testing procedure before RT to the neck [22]. Similarly in breast carcinoma patients who are planned to have supraclavicular field radiotherapy thyroid function tests should be evaluated. In this study we compared thyroid DVHs planned in MVCT-based image guidance aspect of helical tomotherapy which is an IMRT technique and 3-D conformal RT in breast cancer. The use of IMRT to treat the whole breast or chest wall has been shown to improve both dose homogeneity and target coverage as well as to reduce dose to normal tissue when compared with conventional treatment [23]. Limited number of studies has shown that with new treatment techniques (3-D conformal RT and IMRT) thyroid gland is exposed to more radiation dose [3,24]. Reinertsen et al. have shown that the oblique field used for covering the cranial part of the target volume in the 3-D conformal RT technique is unconventional and resulted in an increased dose to the thyroid gland. However, precisely because thyroid doses with the 2-D conventional and 3-D conformal RT techniques differed, a comparison between these techniques seemed reasonable in the context of understanding a possible dose-effect relationship in development of post-breast cancer hypothyroidism. In our study the thyroid volume receiving more than 30 Gy radiations was smaller in Tomotherapy planning comparing to 3-D conformal radiotherapy. This result shows that thyroid tissue can be better protected with different treatment modalities. Similarly, other studies indicate that the greater volumes of normal tissues such as lung and heart receive

lower radiotherapy doses with tomotherapy [25]. In our study, the mean radiotherapy dose to contralateral breast was 6.2 Gy. In literature it was reported that when contralateral breast was completely blocked, as the dose received was reduced the treatment time was prolonged. Because of these drawbacks, the studies on TomoDirect-3DCRT and TomoDirect-IMRT (TomoDirect-3DCRT and TomoDirect-IMRT plans were generated with Tomotherapy Hi-Art version 4.0.4 TPS) are still going on to protect normal tissues during breast radiotherapy with tomotherapy. In a study it was shown that with TomoDirect-3DCRT, not only the dose received by controlateral breast and lungs were reduced but alsothe therapy time was shortened [26]. These developments in tomotherapy plans may make tomotherapy a choice when IMRT is preferred during breast radiotherapy since it both protects thyroid gland and reduces low dose volumes of other organs.Treating breast cancer with tomothreapy seems to decrease hypothyroidism risk it may also increase the risk of thyroid cancer since tomothreapy exposes larger volumes of thyroid with less than 30 Gy of radiation as shown by our study. Ronnkers et al. [27] reported convincing evidence for a nonlinear dose response at thyroid doses exceeding 30 Gy for thyroid cancer. Additionally they found excess relative risk for thyroid cancer per gray at low doses with a wide confidence interval [27]. Breast cancer increasingly effects younger patient population and can be diagnosed in earlier stages with screening programs. Similar studies in breast cancer patients are needed to prevent thyroid carcinoma as a secondary carcinoma and to prevent hypothyroidism or detect it early for the sake of better life quality. In our study the breast cancer patients were treated with 3-D conformal radiotherapy technique and they are followed up for their thyroid function tests and thyroid ultrasonography. The result of follow up will be presented later. As screening for thyroid function has not been a routine in breast cancer survivors. National Comprehensive Cancer Network guidelines suggest routine screening of thyroid function within the first year after radiation therapy in Hodgkin disease and head and neck cancer patients, if radiation treatment fields include the neck [28]. Breast cancer patients have more frequent contact with the health care services, which may explain their increased diagnosis of fatigue [29]. The diagnosis of hypothyroidism is usually reached during this investigation especially in endemic areas for thyroid diseases. The late effects of radiotherapy on thyroid gland and relations with breast cancer and thyroid diseases are not investigated. In supraclavicular field radiotherapy for breast cancer the volume of thyroid gland receiving either more than 30 Gy or less than 30 Gy should be kept in minimum. For this purpose different planning modalities can be utilized Future studies that focus on the effect of these potential modifiers to radiation dose to the thyroid may be warranted.

Conflict of Interest Statement

All authors state that there is no financial or personal relationship with other people or organizations that could inappropriately influence this study.

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