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Comparison the Difference of Thyroid Function Status between 2D & 3D CRT Treatment Technique in HNC Patients

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Abstract **Original Research Article**

Introduction*:** Thyroid gland is an important endocrine gland which regulates metabolic activities in our body as well as regulates vital body functions including breathing, heart rate, central and peripheral nervous systems, body weight, menstrual cycle, cholesterol levels and much more. As thyroid gland placed in the same field area treated by radiation therapy of non-thyroid head and neck cancer patient, so it is a challenge to preserve the normal thyroid function after completion of treatment. ***Objective*:** To assess the comparison the difference of thyroid function status between 2D & 3D CRT treatment technique in HNC patients. ***Methods*:** It was a quasi-experimental study was conducted at National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka, Bangladesh from November 2016 and ended in October'2017. Total of 60 patients with above mentioned criteria were selected and each arm got 30 patients. Patient with histopathology report proven carcinoma of head and neck receiving radiotherapy were selected from tumor board of NICRH. The present study were carried out on patients with biopsy proven malignancies of head and neck who attended the Radiotherapy Department for radiotherapy and who met the selection criteria of the study. ***Results*:** Total study population was 60 among which 30 were in arm A (2D) and 30 were in arm B (3D). Majorities of the patients in arm A were 41-50 years old (46.7%). The mean age of the arm A patients was 52.27 (±7.38) years and that of the arm B was 49.50 (± 13.55) years. Thirty patients of head & neck cancers were included in arm A of the study, i.e. 2D arm. Out of which 21 (70%) were male and rest 9 (30%) were female. Thirty patients of head & neck cancers were included in arm B of the study, i.e. 3D arm. Out of which 23 (76.7%) were male and rest 7 (23.3%) were female. Most of the patients in both arms were farmers (40% in arm A and 60% in arm B). There were 9(30%) oropharyngeal, 8(26.7%) hypopharyngeal and 13(43.3%) laryngeal cancers in arm A. These number were 7(23.3%), 11(36.7%) and 12(40%) in arm B respectively. Both serum T_3 & T_4 levels were reduced in 6 (20%) and 3(10%) patients respectively and the differences were not significant. After 6 months of follow-up the levels fall in both arms but without any statistical significance ($p>0.05$). However, the mean serum T_4 level across the arms was significantly different both before and after 6 months of EBRT. After treatment the level decreased in both arms. After six months of follow-up, the mean TSH levels rise in both arms but without any statistically significance. ***Conclusion: The thyroid function status in head & neck cancer patient after getting radiotherapy planned in 2D conventional Vs 3D conformal technique. After the EBRT clinical hypothyroidism was found two times higher in arm A than arm B patients. And more arm A patients developed subclinical hypothyroidism.

Keywords: Thyroid Function, 2D & 3D CRT, HNC Patients.

INTRODUCTION

Thyroid gland is an important endocrine gland which regulates metabolic activities in our body as well as regulates vital body functions including breathing, heart rate, central and peripheral nervous systems, body weight, menstrual cycle, cholesterol levels and much more. As thyroid gland placed in the same field area treated by radiation therapy of non-thyroid head and neck cancer patient, so it is a challenge to preserve the normal thyroid function after completion of treatment. Radiotherapy (RT) was used clinically for the first time in 1896, initially, RT was referred to as 'Rontgen therapy,' after the discovery of the X-rays by Wilhelm

Rontgen in 1895 [1]. In those early days of RT, external beam RT (EBRT) with superficial kilovolt (kV) X-rays, in addition to treating some malignant diseases, was mainly used to treat various skin diseases through its anti-inflammatory capacities and infectious diseases, such as tuberculosis, due to the supposed antibacterial activity of X-rays [2]. However, for the treatment of cancer, these early EBRT treatments with rather unreliable treatment units often resulted in severe side effects and/or poor local control. In 2D technique, more fields are used in a relatively simple beam arrangement with no emphasis on beam shaping for normal tissue shielding. In 3D technique, tumor volume and critical structures are drawn on slice by slice CT or MRI images. Beams –eye-views are created from digitally reconstructed radiographs with 3D visualization and plan analysis. Head & neck cancer is histologically heterogeneous and organs at risk have less tolerance to radiation. Treatment planning for advanced head and neck cancer is a problem due to the complex shape of the target which commonly has an irregular concave shape volumes and the need to spare critical organs like the mandible, parotid glands, thyroid gland, spinal cord and normal structures [3]. These organs often lie very close to the target volumes critical structures, head and neck cancer presents a challenge for radiotherapy. Treatment with radiotherapy is curative for many patients with localized disease, but with current radiation techniques, dose is limited by both acute and late side effects and the anatomy of the head and neck region. The transition of radiotherapy for head and neck cancer from 2D to 3DCRT made treatment of cancer easier and beneficial [3]. The thyroid gland is located in the lower region of the neck, in relation to the lower part of the larynx and upper part of the trachea. The gland consists of two lobes, right and left, which are connected through the isthmus [4]. The follicular cells of the thyroid gland synthesize and secrete the hormones thyroxine (T4) and triiodothyronine (T3). These thyroid hormones regulate the metabolism of tissues and organs in man, and are tightly genetically regulated in healthy individuals, as shown e.g. in twin studies [5]. Thyroid hormones also influence most of the pathways of intermediary metabolism. If thyroid hormones are deficient, pathways of carbohydrate, lipid and protein metabolism are slowed, as is pathways' responsiveness to other regulatory factors. Thyroid hormones are also essential for normal body growth and the development of the central nervous system, especially in the pre and postnatal period [6].

MATERIALS AND METHODS

It was a quasi-experimental study was conducted at National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka, Bangladesh from November 2016 and ended in October 2017. Total of 60 patients with above mentioned criteria were selected and each arm got 30 patients. Patient with histopathology report proven carcinoma of head and neck receiving radiotherapy were selected from tumor board of NICRH. The present study were carried out on patients with biopsy proven malignancies of head and neck who attended the Radiotherapy Department for radiotherapy and who met the selection criteria of the study. Then all these patients were categorized in two Arms (Arm A and Arm B). Each arm got 30 cases. Arm A patients got radiotherapy planned by 2D conventional technique and Arm B patients got radiotherapy planned by 3D conformal technique. Initially baseline thyroid hormone levels of all patients were done. Blood samples were analyzed for serum triiodothyronin ($T_{3,}$ reference range 0.60 -1.81 ng/ml), serum thyroxin (T_4, reference range 4.6 – 12.4 microgram/dl) and serum thyroid stimulating hormone (TSH, reference range 0.5 – 5.1 microIU/ml). After 6 months of completion of radiotherapy both arms patient were evaluated for post treatment above mentioned thyroid function status.

Inclusion Criteria:

a) Histopathologically diagnosed carcinoma patient in head and neck region.
b) Age 18-70 years.
c) Karnofsky performance status more than 70.
d) Adequate hematological, renal and hepatic function.
e) Written informed consent.

Exclusion Criteria:

a) With primary tumors of the thyroid gland.
b) With pre-existing thyroid gland disorders.
c) Previously treated with radiotherapy in head-neck regions.
d) Who underwent a total or subtotal thyroidectomy.
e) Existence of synchronous multiple malignancies.
f) Recurrent cases.
g) Karnofsky performance status less than 70.
h) Other major vital organ dysfunction.
i) Pregnant or Lactating women.

Operational definition:

Two-dimensional (2D) radiotherapy: It consists of a single beam from one to four directions. Beam setups were usually quite simple; plans frequently consisted of opposed lateral fields or four field "boxes".

Three-dimensional (3D) radiotherapy: It is CT-based planning which take into account axial anatomy and complex tissue contours such as the hour glass shape of the neck and shoulders.

Clinical hypothyroidism: It is a condition in which there is elevated TSH level and low thyroid hormone associated with clinical features of hypothyroidism.

Subclinical hypothyroidism: In this condition there is elevated TSH level but thyroid hormone level remain within normal range without obvious feature of hypothyroidism.

Data Analysis

After cleaning and editing, all the relevant data were compiled on a master chart. Statistical analysis of the results was obtained by SPSS for Windows (IBM SPSS Statistics for Windows, version 19.0, Armonk, NY, IBM Corp.). Continuous data were expressed as mean ± SD and were compared by Student "t" test (Table 1). Categorical data were expressed as number and percentage and were compared via the Chi-squared test and Fischer's exact tests. Two tailed $p<0.05$ was considered as significant.

RESULTS

Total study population was 60 among which 30 were in arm A (2D) and 30 were in arm B (3D) (Table I). Majorities of the patients in arm A were 41-50 years old (46.7%). Eleven patients (36.7%) in arm A and 10 patients (33.3%) in arm B were between 51-60 years of age. Least numbers of patients in both arms were aged ≤40 years or >60 years. However, these differences were not statistically significant ($p>0.05$). The mean age of the arm A patients was 52.27 (±7.38) years and that of the arm B was 49.50 (± 13.55) years. No significant difference was observed between these two groups ($p>0.05$). Thirty patients of head & neck cancers were included in arm A of the study, i.e. 2D arm. They were divided into male and female groups. Out of which 21 (70%) were male and rest 9 (30%) were female. Thirty patients of head & neck cancers were included in arm B of the study, i.e. 3D arm. Out of which 23 (76.7%) were male and rest 7 (23.3%) were female (Fig-I & II). Most of the patients in both arms were farmers (40% in arm A and 60% in arm B). There were 9(30%) oropharyngeal, 8(26.7%) hypopharyngeal and 13(43.3%) laryngeal cancers in arm A. These number were 7(23.3%), 11(36.7%) and 12(40%) in arm B respectively. In arm A 25 (83.3%) were suffering from stage III disease. Remaining five (16.7%) had stage IVA disease. In arm B all 30 patients had stage III diseases. This difference was statistically not significant ($p>0.05$).

Table I: Comparison of age between two groups (N=60)

Category	Mean (±SD) (years)	t-value	df	p-value
Arm A (2D)	52.27 (± 7.38)	0.982	44.798	0.331
Arm B (3D)	49.50 (± 13.55)			

2D =Conventional two dimensional radiotherapy; 3D= CT based three dimensional conformal radiotherapy; SD= Standard deviation; df= Degree of freedom.

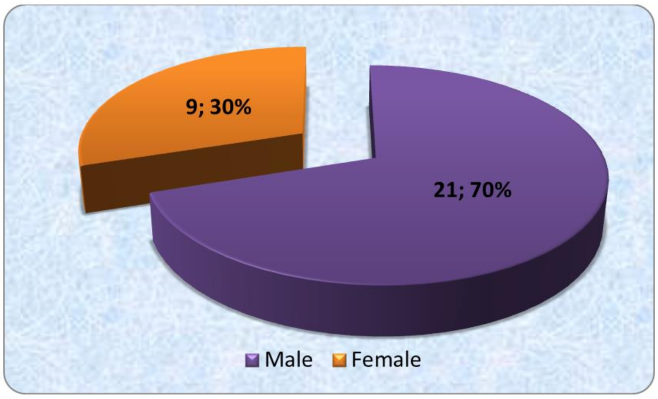

Figure 1: Pie chart showing sex distribution of arm A (2D)

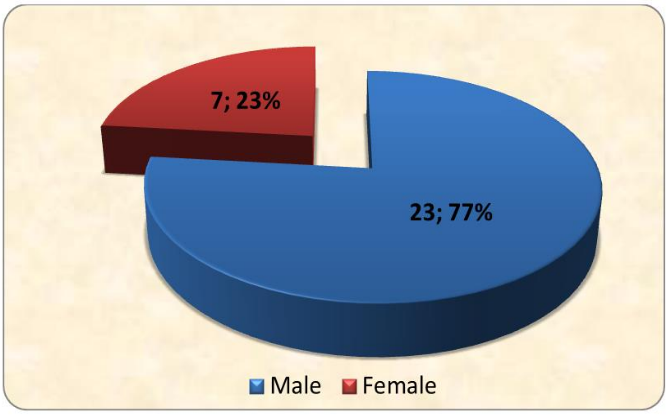

Figure 2: Pie chart showing sex distribution of arm B (3D)

Table II: Distribution of the patients by presence or absence of hypothyroidism (N=60)

Diagnosis	Category of treatment		Chi-squared test	*p*-value
	Arm A (2D)	Arm B (3D)		
Clinical hypothyroidism	06 (20.0)	03 (10.0)	2.639	0.267
Subclinical hypothyroidism	8 (26.7)	05 (16.7)		
Normal thyroid function	16 (53.3)	22 (73.3)		
Total	**30 (100.0)**	**30 (100.0)**		

Table II shows the distribution of the patients by presence or absence of hypothyroidism. Clinical hypothyroidism was present six (20%) and three (10%) patients in arm A and arm B respectively. Comparatively more arm A patients (8, 26.7%) developed subclinical hypothyroidism than arm B patients (5, 16.7%). However, this difference was statistically not significant (p>0.05).

Table III: Distribution of the patients by thyroid hormones status (N=60)

Parameter	Category of treatment		Chi-squared test	p-value
	Arm A (2D)	Arm B (3D)		
TSH level				
Normal	16 (53.3)	22 (73.3)	2.5837	0.108
Raised	14 (46.7)	8 (26.7)		
T3 level				
Normal	24 (80.0)	27 (90.0)	1.1768	0.278
Reduced	6 (20.0)	3 (10.0)		
T4 level				
Normal	24 (80.0)	27 (90.0)	1.1768	0.278
Reduced	6 (20.0)	3 (10.0)		

(T_3, reference range 0.60 -1.81 ng/ml), serum thyroxin (T_4, reference range 4.6 – 12.4 microgram/dl) and serum thyroid stimulating hormone (TSH, reference range 0.5– 5.1 microIU/ml)

Table III shows the distribution of the patients by thyroid hormones status. In 14 (46.7%) patients of arm A serum TSH level was raised above normal range while serum TSH level was increased in only 8 (26.7%) arm B patients. Statistically this difference was not significant. Both serum T_3 & T_4 levels were reduced in 6 (20%) and 3(10%) patients respectively and the differences were not significant.

Table IV: Comparison of thyroid hormone levels between two arms (N=60)

Variables	Treatment arm	Mean	Std. Deviation	t-value	*p*-value
Serum T_3 before EBRT	Arm A (2D)	1.207	0.324	0.973	0.36
	Arm B (3D)	1.141	0.189		
Serum T_3 after 6 months of follow-up	Arm A (2D)	0.834	0.276	1.692	0.096
	Arm B (3D)	0.725	0.220		
Serum T_4 before EBRT	Arm A (2D)	8.037	2.696	-2.595	0.013
	Arm B (3D)	9.409	1.054		
Serum T_4 after 6 months of follow p	Arm A (2D)	5.666	2.428	-2.766	0.008
	Arm B (3D)	7.167	1.716		
TSH level before EBRT	Arm A (2D)	3.664	1.444	-0.106	0.916
	Arm B (3D)	3.693	0.415		
TSH level after 6 months of follow-up	Arm A (2D)	8.2617	5.667	1.952	0.056
	Arm B (3D)	5.906	3.406		

Table IV shows the comparison of thyroid hormones between two arms. Before EBRT the mean serum T_3 level across the arms was not significantly different. After 6 months of follow-up the levels fall in both arms but without any statistical significance (p>0.05). However, the mean serum T_4 level across the arms was significantly different both before and after 6 months of EBRT. After treatment the level decreased in both arms. After six months of follow-up, the mean TSH levels rise in both arms but without any statistically significance.

DISCUSSION

Total sixty patients were categorized in two Arms (Arm A and Arm B). Each arm got 30 cases. Arm A patients got radiotherapy planned by 2D conventional technique and Arm B patients got radiotherapy planned by 3D conformal technique. In this study, the mean age of the arm A patients was 52.27 (±7.38) years and that of the arm B was 49.50 (± 13.55) years. In arm A 21 (70%) patients were male while in arm B there were 23 (76.7%) male patients. These patient characteristics were similar to other studies published [7, 8]. In this study, it was found that in arm A clinical hypothyroidism was mainly found in 41-50 year age group (3/6); two patients were 51-60 years age group. In arm B 80% patients developing clinical hypothyroidism were in the age group of 61-70 years. However, statistically the differences were not significant (p>0.05). Colevas *et al*., stated that there was an increased incidence in patients with age more than 60 years [9]. Hancock *et al*., stated that the relative risk of primary hypothyroidism decreased by a factor of 0.99 with each additional year of age [10]. It was found that in both arms clinical hypothyroidism was mainly found in females (66.7%). This finding is consistent with other study findings. Posner *et al*., stated that female sex has been associated with 20% increased hypothyroidism and Hancock *et al*., observed an increased relative risk of 1.6: 1 in females [10, 11]. In this study, the maximum follow-up period was 6 months post-RT, which is much lower than the majority of studies. Tell *et al*., followed up patients up to 3 years; Turner *et al*., had a mean follow-up of 21 months [7, 8, 12]. In the current study clinical hypothyroidism was present six (20%) and three (10%) patients in arm A and arm B respectively. Comparatively more arm A patients (8, 26.7%) developed subclinical hypothyroidism than arm B patients (5, 16.7%). However, this difference was statistically not significant. The earliest follow-up was done by Aich who evaluated the thyroid status at 6-week post-RT. They noticed a 4.2% incidence of clinical hypothyroidism at 12 months and not earlier [12]. The incidence rate is high in our study when compared with other studies. The incidence in studies varies from 3 to 40%. Colevas *et al*., noted that 50% of the patients who developed hypothyroidism did so in the first year [9]. Emami *et al*., reported different tolerance values of 8/5, 13/5, and 35/5 (incidence of clinical hypothyroidism in 8%, 13%, and 35% of patients at 5 years) at the level of 45, 60, and 70 Gy, respectively [13]. This is one of the few studies which had a high incidence at first year. Most studies however have a lower rate even after the end of the second year. Tell *et al*., found that the Kaplan-Meier predictive risk for hypothyroidism after 5- and 10-year post-irradiation was only 20% and 27%, respectively [14]. Aich had an incidence of 16.6% at the end of 2-year follow-up [8]. It was found that before EBRT the mean serum T_3 level across the arms was not significantly different. After 6 months of follow-up the levels fall in both arms but without any statistical significance (p>0.05). Six months after RT, the mean TSH levels rose in both arms but without any statistically significance. Before EBRT the mean serum T_3 level was 1.207 and after 6 months of follow-up the level fall to 0.834 in arm A. Before EBRT the mean serum TSH level was 3.664 and after 6 months of follow-up the level raised to 8.262. All the differences were statistically highly significant (p<0.001). In arm B, before EBRT the mean serum T3 level was 1.141 and after 6 months of follow-up the level fall to 0.725 while before EBRT the mean serum TSH level was 3.693 and after 6 months of follow-up the level increased to 5.906. All the differences were statistically highly significant (p<0.001). In general, it seems that external irradiation of the normal thyroid may cause dysfunction of the gland within months to years following treatment. The study with the longest follow-up of patients was that presented by Einhorn and Wikholm. With 10-year follow-up in 41 patients of carcinoma of the larynx and hypopharynx treated with RT the incidence of established hypothyroidism was 7.3% [15].

Conclusion

Hypothyroidism (clinical or subclinical) is a frequently ignored but a significant complication of external beam irradiation to the neck. The thyroid function status in head & neck cancer patient after getting radiotherapy planned in 2D conventional Vs 3D conformal technique. After the EBRT clinical hypothyroidism was found two times higher in arm A than arm B patients. And more arm A patients developed subclinical hypothyroidism. In the present study hypothyroidism was noted within six months following RT.

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