Biochemical Outcome of Repeated Radioactive Iodine Therapy in Patients with Primary Hyperthyroidism– Follow Up of a Decade

Sharmin Reza[1], AzmalKabir Sarker[2,3], Farhana Haque[1], Mohammed Mehedi Al Zahid Bhuiyan[4], Simoon Salekin[1], Papia Akhter[1]

[1]National Institute of Nuclear Medicine and Allied Sciences, BAEC, BSMMU campus, Shahbag, Dhaka

2Institute of Nuclear Medicine and Allied Sciences, Mitford, SSMCH campus, Dhaka

[3]Institute of Nuclear Medical Physics, Atomic Energy Research Establishment, Savar, Dhaka

[4]Institute of Nuclear Medicine and Allied Sciences, SOMC campus, Sylhet

Correspondence Address: Dr. Sharmin Reza,Assistant Professor& SMO, National Institute of Nuclear Medicine and Allied Sciences, BSMMU campus, Shahbag, Dhaka-1000, Bangladesh. rezasharmin19@gmail.com

ABSTRACT

Background: Whileradioactive iodine therapy (RAIT) in patients with primary hyperthyroidism results in euthyreosis or hypothyreosis, requirement of repeated therapy in a proportion of patients is a clinical reality. This study describesbiochemical outcomeof patients requiring repeated RAIT and the dose profiles across the demographic traits.

P***atients and Methods:*** The study retrospectively included the patients who underwent RAIT for Primary hyperthyroidism from January to December of 2006, using a modified fixed dose protocol following an institutional guideline which was adopted as the national guideline in 2007. Persistence of biochemical features of hyperthyroidism six months after RAIT was an indication for repeated therapy. Follow up data of eligible patients till December of 2016 was included in the descriptive statistics.

Results: One, Two, three and four instances of RAIT were given to 83%, 14%, 2% and ≤ 1% of patients resulting in hypothyroidism to 58%, 67%, 67% and 100% of patients after each instance of therapy with incremental dose. Apparently more females than males ended up as biochemically hypothyroid, though not significant (OR 1.15, p=0.56).Younger females became significantly hypothyroid (p = 0.03).Patients with euthyroid outcome received higher dose-1of RAIT (P=0.007) which was found significant in females (p=0.005), in patients with Graves' disease (GD) (p=0.018) and in patients receiving two instances of RAIT (p=0.03). Among the patients with GD, Single Toxic Nodule (STN) and Multi-Nodular Goiter (MNG), the proportion of hypothyroid outcome were 61%, 67% and 35%, at ten years following first dose. GD and STN required RAIT for up to four instances.MNG received an apparently higher mean of dose -1 and apparently less steep increment of doses, in comparison to GD and STN.

Conclusion: Thisobservationof patient outcome over a decade was a scope to compare the mentioned guideline's performance with the targets set by influential guidelines and recent reports around the globe.

Key words: **Primary Hyperthyroidism, Radioactive iodine therapy, Repeated dose, Biochemical Outcome.**

Bangladesh J. Nucl. Med. Vol. 22 No. 2 July 2019

Doi: https://doi.org/10.3329/bjnm.v22i2.51762

INTRODUCTION

The reported incidence of hyperthyroidism (HT) in cross-sectional case series from Bangladesh isaround 1%(1, 2). Like most other countries in the world, radioactive iodine therapy (RAIT) has been a second-line treatment for primary hyperthyroidism in Bangladesh for the past five-decade with reportedly satisfactory short term outcomes(3-5). Data from large cohort showed a cumulative incidence of hypothyroidism after RAIT observed over 30 years in patients with Graves' disease (GD) to be more than 80%, while it remained less than 40% in patients with toxic nodular goiter (3). In smaller cohorts with uncategorized diagnoses, the incidence of hypothyroidism following RAIT was up to 40% at one year (6-9). Repeated administration of RAIT may be required in patients with HT (9) which is reported to be 12% in a cohort comprising solely of GD and 23% in another mixed cohort consisting of GD, multinodular goiter (MNG) and solitary toxic nodule (STN) (10,11). The proportion of patient requiring repeated-dose has been reported to be 7% in a study from Bangladesh while 6% required two doses and 1% required three doses (12). This study was designed to analyze and describe the biochemical outcome alongside the dose profile of RAIT administered in patients with HT, observed over a period of 10 years at National Institute of Nuclear Medicine and Allied Sciences (NINMAS), Dhaka, Bangladesh which is the largest thyroid referral center of the country.

PATIENTS AND METHODS

This was a retrospective study, performed in 2018 at NINMAS. Included were all consecutive patients who had undergone RAIT from January to December of 2006, with a clinical diagnosis of Primary hyperthyroidism refractory to anti-thyroid drugs as determined by their referring physicians who were endocrinologists, otolaryngologists, or internal medicine specialists. Pre-therapy work-up for each of the patient, dose determination for initial RAIT, determination of requirement for repeated RAIT and the dose for repeat RAI all were done according to the institutional guideline of NINMAS which was adopted as the national guideline in 2007(13). All patients underwent RAIT with open-source ^{131}I sodium iodide solution using a modified fixed-dose protocol. Persistence of biochemical features of HT after six months of RAIT was an indication for repeated RAIT. Patients were followed up according to the institutional protocol. Follow up data of each patient till December of 2016 was included in statistical analysis.

All relevant demographic and clinical data were entered into analyses. Biochemical outcome categories were compared against age, gender, clinical diagnoses, and dose profile. Categorical data were presented as frequencies and percentages. Continuous data were presented as means and standard deviations (SD) and value ranges. Means were compared using independent sample T-test.

RESULTS

Patient characteristics

Total 321 patients (Female/Male: 190/131) with a mean age of 40.5 ± 13.5 years underwent RAIT within the aforementioned specified period of 12 months. Forty (12.5%) patients dropped out after the first follow up. Mean age of remaining 281 who were eligible for final analysis was 40.2±13.3 years (10 yrs.-79 yrs.). With the other proportions asshown in table-1, a higher number of femalesended up with biochemical hypothyroid status(OR 1.15, 95% CI 0.7-1.8) which, however, was not of statistical significance (p = 0.56).

Smaller proportion of patients required higher instances of dose (table-1 and figure 1), with a higher proportion of patients becoming hypothyroid after repeated RAIT with incremental dose. This data in figure-1 shows the proportions of turning biochemically hypothyroid increased from 58% following a single instance of RAIT to 67% after two, remaining 67% after three and then reaching 100% after four episodes of RAIT.

Table 1: Demographic and clinical characteristics of the eligible patients

Variables	Female	Male		Total
Number	165 (59%)	116 (41%)		281
Age in years	39.9±14.0	40.5±12.4	(p = 0.8)	40.2±13.3
Diagnostic category				
Graves' disease	148	104		252 (90%)
Multinodular goiter	10	7		17 (6%)
Single toxic nodule	7	5		12 (4%)
RAIT frequency				
Once	140	94		234 (83.3%)
Twice	20	19		39 (13.9%)
Thrice	4	2		6 (2.1%)
Four times	1	1		2 (0.7%)
Biochemical outcome				
Euthyroid	64	49		113
Hypothyroid	101 (61%)	67 (58%)	(p = 0.56)	168(59.8%)

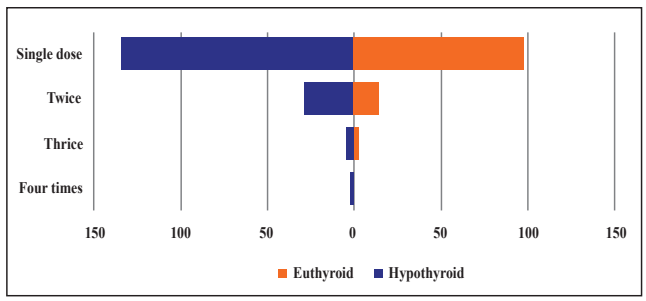


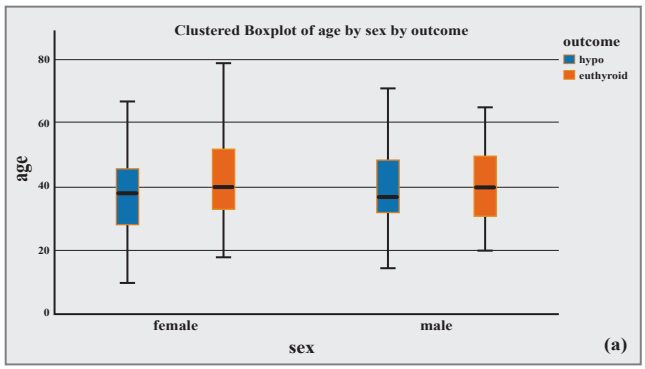
Figure 1: Distribution of post-therapy biochemical outcomesamong dose frequencies. Outcomes are hypothyroid (H, blue on left side) and euthyroid (E, yellow on right side). Single dose of RAIT was given in 234 (E/H: 98/136), two doses in 39 (E/H: 13/26), three doses in six (E/H: 2/4) and four doses in two (both hypothyroid) patients. Hypothyroid outcome was achieved with single dose 58%, two doses 67%, three doses 67% and four doses 100%.

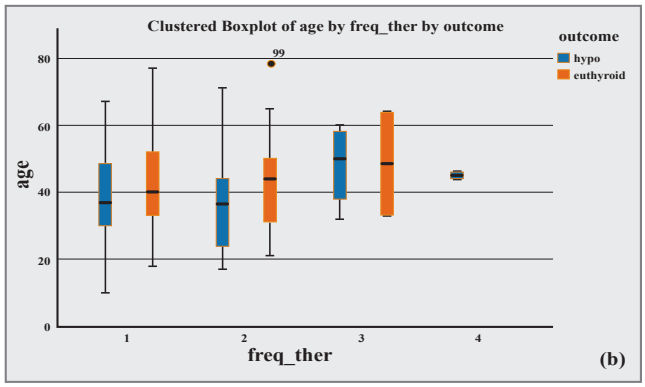
Biochemical outcome and dose profile by age

There was no statistically significant difference among the mean age of both genders (independent sample T-test p = 0.8, Table 1) until the mean ages were further categorized according to biochemical outcomes (Table 2). The younger patients (with lower mean of age) from both genders, from all dose frequencies and from all diagnostic categories tended to end up as hypothyroid (figure 2). However, significantly lower mean of age was seen in females who became hypothyroid (p = 0.03, Table 2) in comparison to those females who became euthyroid following RAIT.

Table 2: Independent sample T-test of mean age among outcome categories cross-tabulated against gender, diagnoses and RAIT incidence

	Hypothyroid	Euthyroid	p
Total	38.8±13.0	42.3±13.6	0.03
Gender			
Female	**38.1±13.5**	**42.9±14.5**	**0.03**
Male	39.8±12.3	41.3±12.5	0.5
RAIT frequency			
Once	38.8±12.7	41.9±13.1	0.6
Twice	36.9±14.9	43.4±17.1	0.2
Thrice	48.0±12.6	48.5±21.9	0.9
Four times	45.0±1.4	n=0	-
Diagnostic category			
GD	38.5±12.7	41.3±13.2	0.9
STN	43.4±17.5	55.0±11.3	0.3
MNG	39.7±15.4	46.3±16.2	0.4





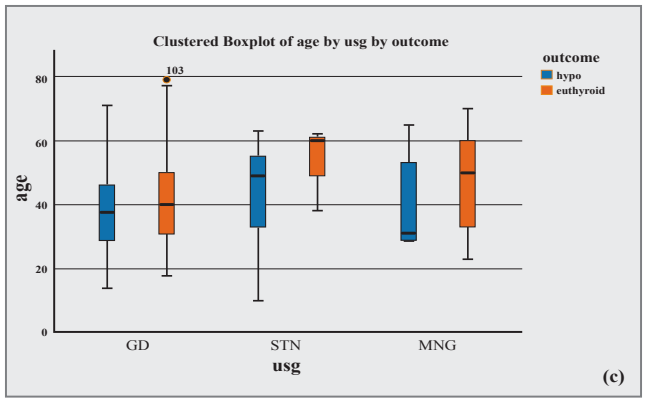


Figure 2: Hypothyroid outcome in younger patients by clustered boxplot among- (a) genders, (b) RAIT dose frequencies and (c) diagnostic categories

Biochemical outcome and dose profile by gender

A possible association of higher risk of the hypothyroid outcome in female patients with a higher amount of administered dose was checked. As shown in table-3, among the gender categories, there was no significant difference in mean administered amount of radioactivity for each dose instance. However, among the biochemical outcome categories, theeuthyroid outcome was found to be associated with a higher mean of dose-1 (p = 0.007, Table 3). Further analysis revealed a significantly higher mean of dose-1 in female gender who ended up as euthyroid (p = 0.005, Table 4).

Table 3: Results of Independent Sample T-test of mean dose among gender categories and outcome categories

	Female	Male	p	Hypothyroid	Euthyroid	p
RAIT Dose (mCi)						
Dose 1	10.9±1.6	11.0±1.8	0.6	**10.8±1.7**	**11.3±1.7**	**0.007**
Dose 2	13.6±2.5	12.8±1.9	0.2	13.0±2.1	13.6±2.5	0.3
Dose 3	18.0±2.7	15.0±3.0	0.2	16.2±3.2	19.0±1.4	0.2
Dose 4	20(n=1)	25(n=1)	-	22.5±3.5	n=0	-

Table 4: Results of Independent Sample T-test of mean dose among gender categories cross-tabulated against outcome categories

		Hypothyroid	Euthyroid	P
Male	Dose 1	11.1±2.1 (n=67)	10.9±1.4 (n=49)	0.6
	Dose 2	12.3±1.8 (n=13)	13.4±1.9 (n=9)	0.2
	Dose 3	13.5±2.1 (n=2)	18.0 (n=1)	0.3
	Dose 4	25.0 (n=1)	-	
Female	Dose 1	**10.5±1.4** (n=101)	**11.6±1.9** (n = 64)	**0.005**
	Dose 2	13.5±2.2 (n=19)	13.8±3.4 (n =6)	0.8
	Dose 3	17.5±2.9 (n=4)	20.0 (n=1)	0.5
	Dose 4	20.0 (n=1)	-	

Biochemical outcome and dose profile by diagnoses

The proportion of patients ended up as hypothyroid was 61% in GD, 67% in STN and 35% with MNG (Figure 3) at ten years following the first dose of RAIT.In this series, up to four doses were administered in patients with GD as well as in patients with STN but the patients with MNG were administered with up to three doses. Compared to GD and STN, patients with MNG received a higher mean of dose-1 although the increment being less steep for subsequent doses (Table-5). Further analysis revealed a significantly higher mean of dose-1 in patients with Graves' disease with the euthyroid outcome (p = 0.02, Table-6).

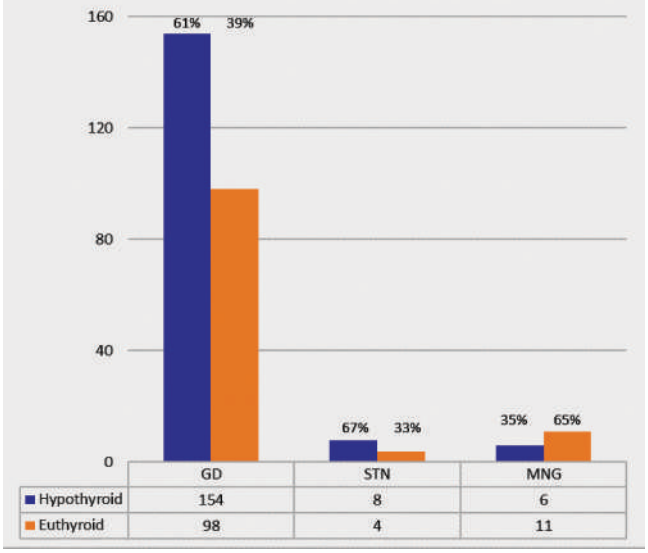


Figure 3: Distribution of biochemical outcomes among diagnostic categories

Table 5: Required number ofRAI doses and administered amount of I-131 in diagnostic categories

	Dose 1	Dose 2	Dose 3	Dose 4
GD	10.6±1.1 (n=252)	12.6±1.8 (n=39)	14.2±1.5(n=4)	25 (n=1)
STN	13.3±2.3 (n=12)	16.7±2.9 (n=3)	20.0±0(n=2)	20 (n=1)
MNG	**15.5**±1.4 (n=17)	**15.6**±1.3 (n=5)	**19.0**±1.4(n=2)	- (n=0)

Table-6: Results of Independent Sample T-test of mean dose among diagnostic categories cross-tabulated against outcome categories

		Hypothyroid	Euthyroid	p
GD	Dose 1	**10.4±1.1** (n=154)	**10.8±0.9** (n=98)	**0.018**
	Dose 2	12.5±1.6 (n=28)	12.8±2.4 (n=11)	0.67
	Dose 3	14.3±1.5 (n=4)	(n=0)	
	Dose 4	25.0 (n=1)	(n=0)	
STN	Dose 1	13.0±2.8 (n=8)	14.0±0 (n=4)	0.51
	Dose 2	16.7±2.9 (n=3)	(n=0)	
	Dose 3	20±0 (n=2)	(n=0)	
	Dose 4	20.0 (n=1)	(n=0)	
MNG	Dose 1	15.8±2.0 (n=6)	15.3±0.9 (n=11)	0.44
	Dose 2	15.0 (n=1)	15.8±1.5 (n=4)	0.69
	Dose 3	(n=0)	19.0±1.4 (n=2)	
	Dose 4	(n=0)	(n=0)	

Doses' profile and analysis of Dose-1

The administered radioactivity rose forsubsequent doses, as reflected by the increasing median per dose (figure 4) and increasing mean per dose (Table 7) with the maximum remaining as 20 mCi until dose-3 then reaching to 25 mCi at dose-4.Table 7 shows the mean (± SD) of doses (mCi) for RAIT as 10.9 ± 1.6 in single therapy; 10.8 ± 1.9 and 12.9 ± 1.9 in cases those required two therapies; 12.7 ± 2.3, 15.2 ± 3.2 and 17.2 ± 2.5 in cases receiving three therapies and 12.0 ± 2.8, 12.5 ± 3.5, 16.0 ± 5.7 and 22.5 ± 3.5 respectively while four therapies were given (Table 7). The mean of dose-1for each biochemical outcome categories were compared among patients grouped on the basis of administered dose instances of RAIT (Table 8). The mean of dose-1was significantly higher in patients with euthyroid outcomes who received up to two doses of RAIT. Off note, the means of other doses were not significantly different among outcome categories (data not shown).

As shown in Table 1, a smaller proportion of patients received an incremental dose of RAIT, with two doses required in 14%, three in 2% and four in ~1%, a trend that remained similar among gender categories (Table 1), diagnostic categories (Table 4) and biochemical response categories (Figure4). Additionally, independent sample T-test (Table 3) shows a significant difference in mean dose at the first instance of RAIT among biochemical outcome categories (p = 0.007). Apparently those with euthyreosis received slightly higher dose-1 in comparison to those with hypothyreosis.

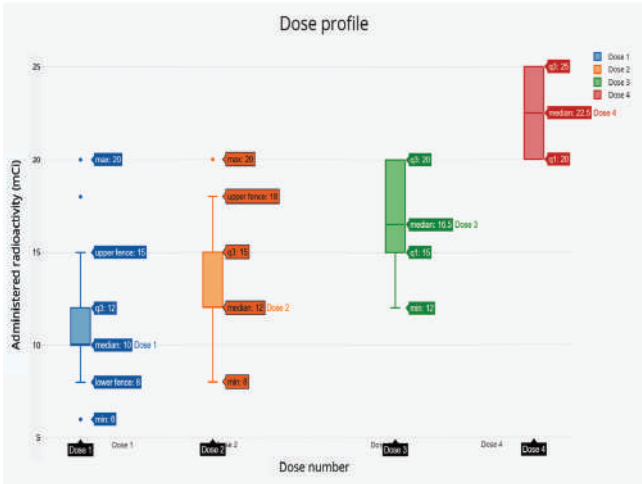


Figure 4: Box plot showing increment of administered radioactivity with subsequent doses; the medians were 10, 12, 16.5 and 22.5 mCi respectively.

Table 7: The mean (± SD) of administered radioactivity (mCi) for each dose of RAIT

RAIT frequency	Dose 1	Dose 2	Dose 3	Dose 4
Once	10.9 ± 1.6			
Twice	10.8 ± 1.9	12.9 ± 1.9		
Thrice	12.7 ± 2.3	15.2 ± 3.2	17.2 ± 2.5	
Four times	12.0 ± 2.8	12.5 ± 3.5	16.0 ± 5.7	22.5 ± 3.5

Table 8: Independent sample T-test for Dose-1 (mCi) among biochemical outcome categories.

	Hypothyroid	Euthyroid	p
Administered dose			
Once	10.8±1.7 (n=136)	11.2±1.6 (n=98)	0.07
Twice	**10.35±1.8** (n=26)	**11.7±1.8** (n=13)	**0.03**
Thrice	11.5±1.9 (n=4)	15.0±0 (n=2)	0.59
Four times	12±2.8 (n=2)	(n=0)	-

DISCUSSION

The cumulative incidence of hypothyroidism in this series, was 59.8%, comparable with that of 50.7% in 272 patients with GD from a recent report (14). An increasing proportion of patient becoming hypothyroid after repeated RAIT with incremental dose, to reach a proportion of 100% among the recipients of the fourth instance of RAIT, was also similar to that report, albeit the rates were lower than the current study likely owing to their use of dual fixed-dose comprising of 10 mCi and 15 mCi (14). With the three diagnostic entities combined, the proportions of patients undergoing one, two, three and four instances of RAIT with incremental dose in this series were 83, 14, 2 and ~1% while another series of 203 patients with GD those proportions were 88, 10, 1.5 and 0.5% (15). Single instance of RAIT with modified fixed dose (median of 10 mCi and mean of 10.89 mCi) brought remission in 83% of patients in this series. Contemporary results of single fixed-dose show one-year overall remission rate of 79% from 500 MBq(13.51 mCi) (10) and 93% from 550 MBq (14.86 mCi)(16) while 10-months remission rate was 62% from a mean dose of 106 MBq (2.86 mCi) (calculated to deliver 60 Gy of absorbed dose) (17) and 3-months cure rate was 75% from a mean dose 328 MBq (8.86 mCi) in a modified fixed dose protocol (15).

Though the apparent female gender predilection for hypothyroidoutcome was about to match with a report of 1036 patients followed up over a period of 23 years(18), the odds in the current series did not reach significance in comparison to males.Within same gender, same dose frequency, and same diagnosis, younger females tended to turn hypothyroid following RAIT which is coherent with the reported association of successful RAIT with female gender and younger age (19).

A higher dose-1 has imparted euthyroid outcome in patients with female gender, GD,or the receiver of two instances of RAIT in this series. This fact is unique and draws attention to some reported determinants of post-RAIT hypothyreosiswhich are female gender and administered dose > 600 MBq (>16.21 mCi), (19).The incidences of post-RAIT hypothyreosis from GD, STN and MNG were 61%, 67% and 35%in the current serieswhile those from another 3-years series were 89.5%, 26.8% and 57.1% respectively (20). Thus the goal of attaining hypothyroidism by RAIT in patients with GD and STN (21) was successful in this series with the rest remained euthyroid, indicating favorable treatment outcome which in turn indicates the appropriate standard of institutional practice. The finding of GD requiring RAIT for up to four instancesmay be taken as a call to consider lithium therapy in long standing GD(22).

Coherently, with the goal of MNG treatment as set to attain volume reduction by the influential guidelines (9, 21), the patients with MNGin this series,received an apparently higher mean of dose -1 albeit with anapparently less steep increment of dosesin comparison to GD and STN, that ended up with a 65% of euthyreosis. This deserves a comparison of facts with a series of 93 patients with MNG that used 13 and 16 mCi as first and second dose, estimated from 'Thyroid Volume Reduction algorithm for GD' to end up with euthyreosis in 69% of patients (23).

CONCLUSION

This study by a superficial narration of favorable patient outcome observed over a decade documents the appropriate standard of institutional practicewith adherence to an institutionalmanagement-guideline that later hasevolved as the national guideline. The statistics from this study was used to make a cursory comparison of the national guideline's performance with some eminent reports around the globe.

DISCLOSURE

No competing financial interests exist.

REFERENCES

1. Paul AK, Miah SR, Mamun AA, Islam S. Thyroid disorders in Khulna district: a community based study. Bangladesh medical research council bulletin 2006 Dec;32(3):66-71.
2. Kamrul-Hasan AB, Akter F, Selim S, Asaduzzaman M, Rahman MH, Chanda PK, Mustari M, Alam MS, Siddiqui MN. Thyroid function and autoantibody status in Bangladeshi patients with type 2 diabetes mellitus. Thyroid Research and Practice 2018 Sep 1;15(3):132.

3. Bonnema SJ, Hegedüs L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. Endocrine reviews 2012 Dec 1;33(6):920-80.

4. Hussain R. History and Perspectives of nuclear medicine in Bangladesh. Asia Oceania Journal of Nuclear Medicine and Biology 2016;4(1):55.DOI:10.7508/aojnmb.2016.04.009

5. Begum SM, Nisa L, Sarker AK. Theranostics in Bangladesh: Current Status, Challenges, and Future Perspective. Nuclear medicine and molecular imaging 2019 Apr 1;53(2):102-7.DOI:10.1007/s13139-019-00590-1

6. Shaha AK, Alam MJ, Rashid MA, Hoque MA, Khasru MR, Ahasan HN. Radio-iodine therapy in hyperthyroidism-a study of 50 cases. Journal of Medicine 2008;9(1):27-30. DOI:10.1007/s13139-019-00590-1

7. Mohamed WM, Sayuti SC, Draman N. Hypothyroidism and its associated factors after radioactive iodine therapy among patients with hyperthyroidism in the northeast coast state of Malaysia. Journal of Taibah University medical sciences 2018 Oct 1;13(5):432-7.DOI:10.1016/j.jtumed.2018.06.004

8. Mahmud MK, Jalil S, Rahman AM, Rashid MM, Sultana S, Taher A, Haque L, Fardous J, Nahar K. Etiologies and posttreatment conditions of thyrotoxic patients in Sylhet division, Bangladesh: A clinical series. Avicenna Journal of Medicine 2017 Jul;7(3):125. DOI:10.4103/ajm.ajm_161_16

9. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European thyroid association guideline for the management of Graves' hyperthyroidism. European Thyroid Journal 2018;7(4):167-86. DOI:10.1159/000490384

10. Fanning E, Inder WJ, Mackenzie E. Radioiodine treatment for graves' disease: a 10-year Australian cohort study. BMC Endocrine Disorders 2018, December 1;18(1):94. DOI : 10. Dec1;18(1):94.DOI:10.1186/s12902-018-0322-7

11. Schneider DF, Sonderman PE, Jones MF, Ojomo KA, Chen H, Jaume JC, et al. Failure of Radioactive Iodine in the Treatment of Hyperthyroidism. Ann SurgOncol 2014;21(13):4174–80. DOI:10.1245/s10434-014-3858-4

12. Nahar K, Akhter P. Factors Affecting and Outcome of Radioactive Iodine Therapy in Hyperthyroidism: A study at Institute of Nuclear Medicine & Allied Sciences (INMAS), Sylhet. Bangladesh J Nucl Med 2016; 19(1):19–23. DOI: 10.3329/bjnm.v19i1.35568

13. Begum F, Sultana S, Nahar N, Alam F, Hasan M, Hussain R, Haque M, Nasreen F, Khan MH, Nisa L, Moslem F. Protocol for management of hyperthyroidism by radioactive iodine (RAIT)-SNMB guidelines. Bangladesh Journal of Nuclear Medicine 2015; 18(1):85-8.DOI:10.3329/bjnm.v18i1.34944

14. El-Sayed MA. The incidence of hypothyroidism following the radioactive iodine treatment of Graves' disease and the predictive factors influencing its development. World journal of nuclear medicine 2016 Jan;15(1):30. DOI:10.4103/1450-1147.167582

15. Onimode YA, Dairo DM, Ellmann A. Pattern of presentation of Graves' disease and response to radioiodine therapy in South African men. The Pan African Medical Journal. 2018;29.DOI:10.11604/pamj.2018.29.48.13655

16. Lewis A, Atkinson B, Bell P, Courtney H, McCance D, Mullan K, Hunter S. Outcome of 131I therapy in hyperthyroidism using a 550MBq fixed dose regimen. The Ulster medical journal 2013 May; 82(2):85.PMID: 24082285

17. Hyer SL, Pratt B, Gray M, Chittenden S, Du Y, Harmer CL, Flux GD. Dosimetry-based treatment for Graves' disease. Nuclear medicine communications 2018 Jun;39(6):486-92. DOI:10.1097/MNM.0000000000000826.

18. Boelaert K, Maisonneuve P, Torlinska B, Franklyn JA. Comparison of mortality in hyperthyroidism during periods of treatment with thionamides and after radioiodine. The Journal of Clinical Endocrinology & Metabolism 2013 May 1;98(5):1869-82.DOI:10.1210/jc.2012-3459

19. Boelaert K, Syed AA, Manji N, Sheppard MC, Holder RL, Gough SC, Franklyn JA. Prediction of cure and risk of hypothyroidism in patients receiving 131I for hyperthyroidism. Clinical endocrinology 2009 Jan;70(1):129-38.DOI:10.1111/j.1365-2265.2008.03291.x

20. Beslic N, Licina S, Sadija A, Milardovic R. Incidence of Hypothyreoidism after Radioactive Iodine–I131 Treatment in Dependance of Hyperthyreoidism Etiology and Therapy Dose. Medical Archives 2017 Aug;71(4):270.. DOI:10.5455/medarh.2017.71.270-273

21. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid2016 Oct 1;26(10):1343-421. DOI:10.1089/thy.2016.0229

22. Sekulić V, Rajić M, Vlajković M, Ilić S, Stević M, Kojić M. The effect of short-term treatment with lithium carbonate on the outcome of radioiodine therapy in patients with long-lasting Graves' hyperthyroidism. Annals of Nuclear Medicine 2017 Dec 1;31(10):744-51.DOI:10.1007/s12149-017-1206-z

23. Schiavo M, Bagnara MC, Camerieri L, Pomposelli E, Giusti M, Pesce G, Reitano C, Caputo M, Bagnasco M. Clinical efficacy of radioiodine therapy in multinodular toxic goiter, applying an implemented dose calculation algorithm. Endocrine. 2015 Apr 1;48(3):902-8. DOI:10.1007/s12020-014-0398-4