Analysis of Excellent Response, Persistent Disease and Recurrent Diseases of Radioiodine Treatment on Differentiated Thyroid Carcinoma Patients- 42 Years' Experience at NINMAS

[1]Fatima Begum, [2]Jasmin Ferdous, [3]Zeenat Jabin, [4]Sadia Sultana, [2] Sadia Salam, [5]Shamsun Nahar Bailey, [6]Shamim Momtaz Ferdousi Begum [7]Nurun Nahar

[1]Professor & Head, Thyroid Division, National Institute of Nuclear Medicine & Allied Sciences (NINMAS)
[2]Associate Professor, Thyroid Division, NINMAS
[3] Professor, Thyroid Division & Head, R & D, NINMAS
[4] Professor & Head, Scintigraphy & Nuclear Cardiology, NINMAS
[5]Assistant Professor, Thyroid division, NINMAS
[6] Director & Head, Pet-CT Division, NINMAS
[7] Ex-Director, NINMAS

Correspondence Address : Dr. Fatima Begum, Professor & Head, Thyroid Division, NINMAS, Block-D, BSMMU Campus, Shahbag, Dhaka-1000, Bangladesh. Email: fatima8ninmas@gmail.com

ABSTRACT

Background: Radioiodine treatment in thyroidectomized differentiated thyroid carcinoma (DTC) patients was introduced in the world in 1940s and in Bangladesh in 1980. Long experience of treatment and lifelong follow up of DTC patients with proper documentation of medical records enriched the archive of the thyroid division of National Institute of Nuclear Medicine & Allied Sciences (NINMAS).

Aims: To evaluate the response of radioiodine treatment in DTC patients at NINMAS and analyze the outcome and prognostic factors in this cohort of patients in a single institute of a developing country.

Patients and Methods: This is a retrospective cohort study. A total of 7525 patients with DTC received RAI ablation therapy from 1980-2021 at NINMAS, among them 5448 patients were treated with radioiodine from 1980-2017. Data were obtained from the medical records of 3482 DTC patients who were followed up until 2021 and all relevant data were available. Demographical, histopathological, surgical, radioiodine ablation doses of ^{131}I, serum biomarkers thyroglobulin (Tg), antithyroglobulin antibody (TgAb) and biochemical investigation data were analyzed systematically. Age, gender, tumor size, presence of local and distant metastases at presentation, extrathyroidal extension (ETE), disease recurrence, and cancer-specific survival were also evaluated. Risk stratifications for recurrence and staging were calculated for dosing of radioiodine. The single dose of radioiodine ranged from 30 mCi to 200 mCi was given according to the postsurgical risk assessment. Repeated doses of radioiodine were given in the cases of persistent disease (PD) and recurrent disease (RD).

Results: The median age of DTC patients was 38 years, with a range of 5-87 years (39.90± 12.67 years), with the majority of patients falling within the 30-39 age group. The ratio of female to male was 3.74:1. Compared to the previous decade, patient number increased about 72 and 16-folds in relation to the 1980s and 1990s respectively at this institute. Papillary thyroid carcinoma (PTC) and follicular variant of thyroid carcinoma (FVPTC) together were evaluated in 3311(95.09%) cases and follicular thyroid carcinoma (FTC) was diagnosed in 171(4.91%). Excellent response (ER) was observed by a single dose of radioiodine ablation in 2853(81.94%) and PD and RD were noted in 388(11.14%) and 241(6.92%) respectively. Tg and TgAb levels at pre-therapy state were significantly higher in patients who had PD ($P < 0.000$) and RD ($P < 0.000$).

Conclusion: Significant increase in the number of DTC patients was observed in the last two decades. ER was noted in 81.94% with a single dose of radioiodine. Serum Tg and TgAb are two prognostic factors for disease outcomes showing high Tg and TgAb in PD and RD cases.

Keywords: Differentiated thyroid carcinoma, Radioiodine, Ablation therapy, Long follow up, excellent response, persistent disease, recurrent disease

Bangladesh J. Nucl. Med. Vol. 25 No. 2 July 2022

Doi: https://doi.org/10.3329/bjnm.v25i2.64642

INTRODUCTION

Thyroidectomy followed by radioiodine ablation is the most successful treatment option for differentiated thyroid carcinoma (DTC). Radioactive iodine (RAI) treatment was first introduced in the USA in the 1940s (1, 2). On the other hand, RAI ablation was first introduced for DTC in

the National Institute of Nuclear Medicine & Allied Sciences (NINMAS) in 1980 (3), which is the apex referral institute of Nuclear Medicine in Bangladesh.

In 2021 in the United States of America, estimated new cases 44,280, percentage of thyroid cancer among all new cancer cases was 2.3% (4). The 5-year survival of 98.3% was estimated during 2011-2017 (5). There is a fast-increasing number of patients with thyroid carcinoma about triple to many fold in the last decades all over the world (4, 6, 7,). Though the RAI treatment is a successful area of therapeutic nuclear medicine, there are still controversies and different opinions persist about the low dose or high dose of radioiodine, application of RAI in low, risk groups, the influence of age, sex, ablation thyroglobulin (Tg), thyroglobulin antibody (TgAb) levels on treatment outcomes.

Treatment protocol varies from institute to institute and among countries and management of patient is usually individualized. Because research protocols range so considerably from one study to the next, a straightforward analysis of RAI treatment outcome is near to impossible. We have experience do RAI treatment in DTC over 40 years at our institute.

The objective of this study was to evaluate the long experience of the outcome as excellent response (ER), persistent disease (PD) and recurrent disease (RD) of RAI treatment in DTC patients at NINMAS.

PATIENTS AND METHODS

From 1980-2021, a total of 7525 patients with DTC (Figure-1) received RAI ablation therapy at National Institute of Nuclear Medicine & Allied Sciences (NINMAS) after thyroidectomy.

Retrospective data was obtained from the medical records of 5448 patients who received RAI ablation (RAIA) during the period of 1980 to 2017. Drop out of data had been observed during collecting different variables, so total 3482 patients who had full filled the study criteria had been recruited. Recruited patients received RAI until 2017 and were followed up until 2021. Before the commencement of the study, the research protocol was approved by Medical Research Ethics Committee (MREC), NINMAS. Evaluation of patients' age, sex, histopathological diagnosis, stimulated thyroglobulin (sTg) and TgA levels, parathyroid hormone (PTH), ultrasound (US) imaging of the neck, thyroid bed scan, and radioiodine uptake test on the 15th day of post thyroidectomy had been routinely done.

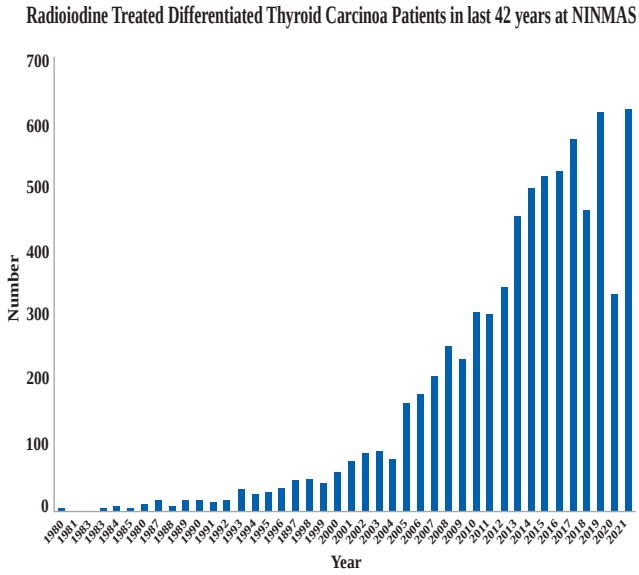


Figure-1. The histogram is showing the year-wise number of patients with differentiated thyroid carcinoma treated with radioiodine therapy at NINMAS since 1980 to 2021.

Risk stratification for recurrence and staging was calculated before therapy by physicians according to previous guidelines, American Joint Committee for Cancer (AJCC), American Thyroid Association (ATA) 2015 guidelines (8), operation notes, and histopathological reports. About 30 m Ci-100 m Ci was given in low-risk and intermediate-risk groups of patients. ATA 2015 guideline recommendations were not to give RAIA to low-risk DTC patients. Previously, a good number of patients of the low-risk group of DTC received RAIA in our institute. Nowadays, we discuss the recommendations about RAIA in low-risk DTC patients. In some patients, risk stratification could not be done clearly due to lack of detail information of operation notes and histopathological reports. Still, some patients of low-risk group are given low dose RAIA upon patients' options. DTC with lymph nodes and lungs metastases received 150 m Ci. DTC patients with bone metastases were given 150-200 m Ci. In a few cases, DTC patients with brain metastases had been treated with 200 m Ci of radioiodine who had prior complete surgical removal of metastases. Thereafter, patients were kept on levothyroxine at TSH suppressive dose after 48 hours of RAIA.

Baseline post-therapy whole-body scan (RxWBS) was usually done on the 5th day of radioiodine ablation to observe the presence of ^{131}I avid thyroid tissue remnants in thyroid bed and presence of ^{131}I avid metastatic lesions in extrathyroidal location. All recorded data were collected in excel sheet and analyzed.

In the first year, each patient was checked three times for clinical evaluation, FT4, TSH, Tg, TgAb, calcium, and US of the neck wherever indicated. After one year of RAIA, a diagnostic whole-body scan by ^{131}I (DxWBS) was performed. A CT scan was performed whenever a CT scan was required or a patient complained of a neck mass or elsewhere, or to further clarify US findings. The Thyroid Division of NINMAS has taken on the responsibility of lifelong follow-up for all the DTC patients who received RAIA here and who are referred to us.

The following criteria are used to assess treatment outcome or response: a) excellent response or no evidence of disease (NED) if patients have no disease-related complaints or no mass at the neck or elsewhere, a serum Tg level of ≤1 ng/ml, and DxWBS is negative. b) Persistent Disease: If patients had clinical complaints, a persistent neck mass, metastatic cervical lymph nodes, distant metastatic lesions in DxWBS or in other imaging, a serum Tg level >10 ng/ml, and lesions proven by FNAC, c) Recurrent disease of DTC was considered when a patient remained disease-free for at least one year or a certain period of time and then again developed metastatic tissue in the thyroid bed, locoregional lymph nodes, or distant metastases (8,9). Subsequent RAI doses were administered in PD and RD, typically resulting in ^{131}I-avid metastases in the lungs and bones observed in RxWBS, DxWBS, or evaluated by US or other imaging modalities, as well as rising Tg. RAI doses were repeated according to the patient's condition, and six monthly therapy was administered until the avidity of metastatic lesions of the lungs and bones subsided, or up to 650 mCi as needed. In cases, where there were dilemmas about the presence of metastases, especially in those patients who showed rising serum Tg in subsequent follow-up but no evidence of metastatic lesions was located by the US, CT, DxWBS, and then PET-CT was recommended to detect metastatic non-iodine avid tissue. All data were preserved in record files; those data were obtained in an Excel sheet for this study accordingly.

Statistical analysis:

Most study variables were expressed as numbers, percentages, means, and standard deviations (SD). We compared and classified patients with ER, PD, and RD. Using the chi-square test, categorical variables (such as sex and diagnosis) were examined. The Mann Whitney-U test, a non-parametric test, was used to evaluate distributions that were not normal for continuous variables (such as age, sTg, and TgAb level), while the student's t-test was used for variables that were regularly distributed. The variables' normality was examined using the Kolmogorov-Smirnov test. SPSS version 26 was employed. P-value lower than 0.05 were regarded as statistically significant.

RESULTS

The age range of DTC patients was 5-87 years, and the mean age was 39.90±12.67 years, with a median of 38 years. Most of the patients presented within 30–39 years, and subsequently, more patients were noted in 40–49 years. Only few patients received radioiodine below 9 and above 80 years (Figure-2).

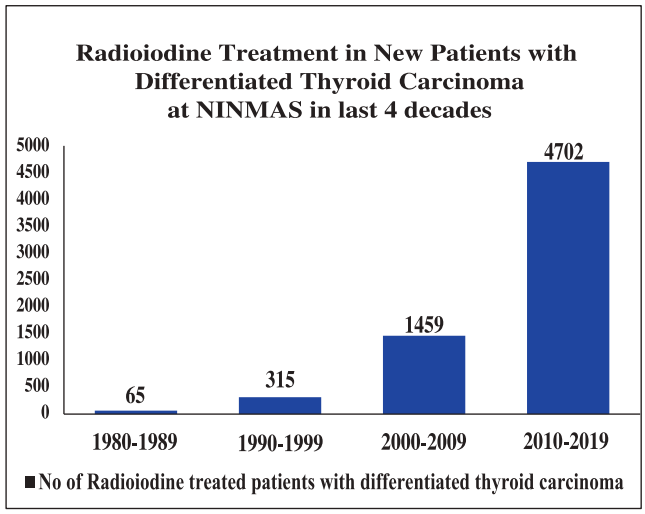


Figure-2: Number of Radioactive iodine treated new patients with DTC in last four decades (decade-wise distribution).

In the last decades, a tremendous increase of RAI treated DTC patients' number at NINMAS has been observed – 16 fold increment of DTC patients was

noted in the last two decades (2000-2019) compared to the patient's number seen in 1980-1999. Patients' numbers in different decades are shown in Figure-3.

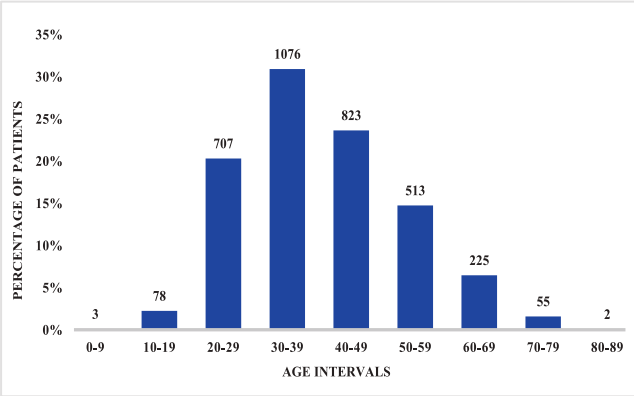
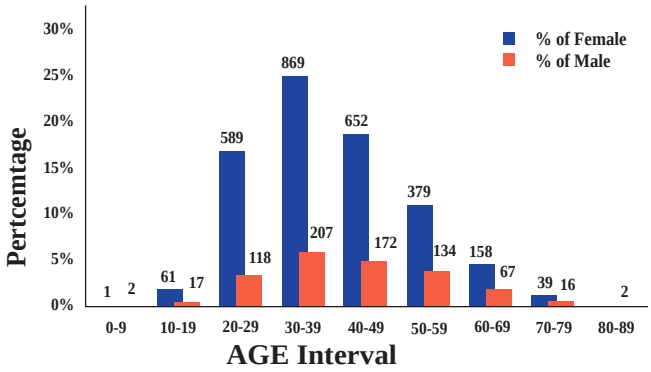


Figure-3: The histogram is showing the percentage of radioiodine treated differentiated thyroid carcinoma patients in different age intervals.

Most of the patients were female 2747(78.89%) and male 735(21.11%) in this study and the female to male ratio is 3.74:1 (Figure-4).



Age Interval	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Female to Male Ratio	0.5:1	3.59:1	4.94:1	4.14:1	3.78:1	2.83:1	2.36:1	2.44:1	0:1

Figure 4: Gender distribution of differentiated thyroid carcinoma patients at different age interval.

Histopathological analysis showed PTC, follicular variant papillary thyroid carcinoma (FVPTC), and FTC were the three main categories evaluated in postsurgical tissue. PTC & FVPTC together were evaluated in 3311(95.09%) and FTC was diagnosed in 171(4.9%).

The outcome of radioiodine treatment was analyzed and their follow-up period was 4 years to 38 years. ER was seen in 2853(81.94%) and ablated by a single dose of radioiodine. PD and RD were noted in 11.14% and 6.92% respectively (Table-I). Multiple doses of radioiodine were given in PD and RD cases. High sTg levels were found in the PD and RD groups than ER group patients (P=0.0000). Higher levels of TgAb were also observed in the PD and RD group (p=0.000) (Table-I).

Table-1: Patient's characteristics and other findings in excellent response (ER) or persistent diseases (PR) or recurrent disease (RD) groups.

	Excellent Response	Persistent disease	Recurrent disease	P-value
Total number of Patients (3482)	**2853 (81.94%)**	**388 (11.14%)**	**241 (6.92%)**	
Age (5– 87 years)				
Mean ± SD	39.40 ± 12.33	41.24 ± 13.98	43.58 ± 13.65*	*0.000
39.90 ± 12.67				
Median	38	40	43	
38				
Sex	F– 2286(80.13%)	F- 283(72.94%)	F –178 (73.86%)	NS
Female- 2747 (78.89%)	M-567(19.87%)	M – 105(27.06%)	M –63 (26.14%)	
Male – 735 (21.11%)	4.03 : 1	2.70 : 1	2.83 : 1	
F/M ratio : 3.74 : 1				
Diagnosis				
PTC- 3311(95.09%)	PTC- 2736 (95.90%)	PTC- 348 (89.69%)*	PTC- 227 (94.19%)	*0.000
FTC-171 (4.91%)	FTC- 117 (4.10%)	FTC- 40 (10.31%)	FTC- 14 (5.81%)	
Tg level (ng/mL)	**2853**	**388**	**241**	0.000
< 2	2226 (78.02%)	218 (56.19%)	126 (52.28%)	
2- 10	454 (15.91%)	68 (17.53%)	51 (21.16%)	
11<100	144 (5.05%)	53 (13.66%)	46 (19.09%)	
100 - 300	14 (0.49%)	21 (5.41%)	13 (5.39%)	
>300	15 (0.53%)	28 (7.21%)	5 (2.08%)	
AntiTg level (IU/mL)	**2853**	**388**	**241**	0.000
<4	286 (10.00%)	44 (11.34%)	31 (12.87%)	
4 - 100	2483 (87.05%)	325 (83.76%)	193 (80.08%)	
100 - 500	84 (2.95%)	19 (4.90%)	17 (7.05%)	
>500	30 (1.05%)	17 (4.38%)	12 (4.98%)	

Reference Category: Complete response. *p <0.05: persistent and recurrent vs complete response. Tg-Thyroglobulin, Tg Ab- antithyroglobulin antibody.

DISCUSSION

It has been observed the number of DTC patients has increased significantly over the past few decades. This might be a result of greater disease awareness, and availability of imaging facilities, especially ultrasound imaging, and treatment options even in developing nations like ours. Incidence of thyroid cancer has substantially increased in developed countries over the past 30 years, and so this increase has been associated to over diagnosis (10), screening, and possibly advances in imaging technologies. Between 1974 and 2013, the incidence of thyroid cancer increased by 3.6% year in the USA (from 4.56 per 100 000 person-years in 1974–1977 to 14.42 per 100 000 person-years in 2010–2013) (11). These results were consistent with the findings of our study.

Among all DTC patients, we had found PTC in 95.09% and FTC in 4.9% cases. In a previous study of Otolaryngology Department of Bangabandhu Sheikh Mujib Medical University, authors obtained data of 154 patients with thyroid carcinoma during the years 1986 and 2000 retrospectively. Among them, DTC was seen in 130 cases, PTC was in 98/130(75.4%), and FTC in 32(24.6%) (12). FTC was reported 10.1% by Aziz et al. in 2021 (13) among all thyroid carcinoma patients recorded from 2010 to 2019. PTC accounted for 83.6% of thyroid cancer cases reported by a surveillance in the United States between 1974 and 2013 and is the most common type of thyroid cancer (11).

A higher risk of FTC has been linked to both iodine deficiency and endemic goiter. A higher incidence of PTC and a reduced incidence of FTC have both been associated with iodine supplementation (14). One thing we have noticed is a decline in the number of FTC referrals at this institute. It might be because Bangladesh's iodine deficiency has decreased after a national salt iodination program was implemented in 1989 (15, 16).

Among all malignancies, only the stage of thyroid cancer is influenced by age (17). In this study, the majority of DTC patients were between the ages of 30-39 years, with very few patients younger than 9 or older than 80 years old. There was no significant difference in age between the two PD groups of ER patients. Older patients were noted in RD groups (P = 0.000). This finding was not in agreement with the findings of another study by Jonklaas et al, which showed that female patients over the age of 55 had a greater incidence of disease-specific survival (DSS) than young male patients (18).

Primary thyroid microcarcinomas (PTMCs) advanced rapidly in young patients than in middle-aged or elderly ones. The researchers found that clinical PTC recurrence is more common in young people (19). Although the patient's DSS may be impacted by their age at diagnosis of DTC (20). The authors of the meta-analysis found that there is no age cutoff that permits risk categorization in DTC patients.

We observed female predominance in this study and female to male ratio was 3.74:1 and there were no statistically significant difference in outcome of RAI ablated DTC patients in respect of gender. Other studies also described the similar findings. Female to male ratio: 3.5:1 was also found by Nilubol N et al (2013) (21), but they observed that men, regardless of age, had lower DSS than women (p-0.01). According to the authors, DTC is 2-4 times more common in females than in males. For PTC, the average age of diagnosis is 40-45 years old, while for FTC it was 50-55 years old. They are extremely uncommon among children (7). In PTC patients, male sex was also associated with statistically significant poor prognosis (22). Other authors observed that male sex was not an independent prognostic predictor of DTC recurrence, according to their multivariate analysis (23).

In the presented study, ER was observed in 81.94%, PD in 11.14% and RD in 6.92% DTC patients after total thyroidectomy and RAI ablation. Despite the fact that DTC is a highly differentiated tumor, disease recurrence or metastasis in DTC patients after surgery is about 10%–30% (24,). Primary management of DTC also rendered 87% of patients disease-free in a Canadian population-based study cohort (25). Barres B et al., 2019 (26) included DTC patients from 1995 to 2010 in their study, with a mean age of 48.9 $\pm$ 14.82 years, a F:M-3.6:1 ratio, having PTC 88.5% and FTC 11.5%,

and they observed long-term remission in 79%, PD in 16.5%, and RD in 4.5%. Pre-ablation Tg threshold was <10 µg/L with an NPV of 84% in favor of long-term remission in their cohort, according to ROC analysis. Similarly, in our cohort, the ER group had more patients with stimulated Tg (sTg) 2 ng/ml than the PD and RD groups. A higher proportion of patients in the PD and RD groups had sTg levels greater than 11 ng/ml. Piccardo et al., (27) validated high levels of ablation-Tg in patients with PD following first therapy in their research and concluded that higher ablation-Tg was the greatest predictor of PD. The authors also observed that in high-risk DTC patients, sTg levels of 50 g/L or more are a useful early predictor of disease persistence/recurrence. High sTg levels of 50 g/L or more were found to be associated with both progression-free survival (PFS) and overall survival (OS) (27).

The 10 ng/ml cut-off level had a sensitivity and specificity of 73%, a positive predictive value of 43%, and a negative predictive value of 89% in identifying patients with PD (28). Liu L 2018 suggested pre-ablation s-Tg level of 156 ng/mL as the optimal cut-off point to predict distant metastases (29). Couto JS, 2020 has found a significant difference in s-Tg levels between patients with and without metastases (P<0.001) (30). Shangguan L 2019 commented that pre-treatment sTg level was found to be an independent prognostic factor for the therapeutic outcome of ^{131}I treatment which is in agreement of our study. After a mean follow-up period of 7.1± 5.3 years, Ng Sc et al. 2017 (31) observed that 20.9% of PTC patients were in non-remission and 79.1% were in remission state. The non-remission group was mostly male, had larger tumors, and had higher serum Tg levels after surgery.

In our study, higher number of DTC patients had TgAb level >100 mIU/ml in PD and RD groups than the ER groups (p-=0.000). Tg levels could be undetectable due to high TgAb levels. As a result, TgAb level tests after complete thyroidectomy and RAI ablation of DTC are valuable for diagnosing PD and RD. Thereby increased TgAb levels following initial treatment are considered a 'biochemical partial response'' (6). TgAb is observed more commonly in PTC patients than in follicular cancer patients (32, 33,)

In their investigation, Spencer and co-authors (34) stated that roughly 20% of DTC patients had elevated TgAb levels. The prevalence of positive TgAb was relatively low, less than 10%, in a study involving a relatively large cohort of patients with DTC and positive TgAb at some point during follow-up. However, the probability of disease recurrence in PTC has been reported to reach 20% at some point during the patient's lifetime. A large increase in TgAb combined with steady TgAb concentrations should be considered a sufficient risk factor for recurrent or persistent illness. A considerable drop in TgAb levels, on the other hand, can be a favorable prognostic sign (35).

On the other hand, elevated blood TgAb levels did not enhance the probability of cancer recurrence or cancer death in PTC patients over long follow-up period observed by authors. In author's experience, TgAb status is not a meaningful prognostic or predictive marker for clinical outcomes in patients with PTC (36).

CONCLUSION

A significantly increasing number of patients with DTC were treated by radioiodine in the last two decades at NINMAS. DTC patients presented with a median age of 38 years and female predominance (F:M-3.74:1). Excellent response was observed in 81.94% of DTC patients by giving single dose of radioiodine. PD and RD were noted in 11.14% and 6.92% respectively. High levels of sTg and sTgAb were associated with PD and RD and might be considered as prognostic factors for disease outcome.

Conflict of interest: The authors declare that there is no conflict of interest.

Acknowledgement: We are thankful to Fariha Zaman Surovi, BSS (Economics, DU), who has helped us in statistical analysis of the data.

REFERENCES

1. de Souza PB, McCabe CJ. Radioiodine treatment: an historical and future perspective. Endocrine-related cancer. 2021 Oct 1;28(10):T121-4.
2. Fahey FH, Grant FD. Celebrating eighty years of radionuclide therapy and the work of Saul Hertz. Journal of Applied Clinical Medical Physics. 2021 Jan;22(1):4-10.
3. Hussain R. History and Perspectives of nuclear medicine in Bangladesh.

Asia Oceania Journal of Nuclear Medicine and Biology. 2016;4(1):55.
4. Cancer Facts & Figures 2022, The American Thyroid Society. Pp;26.
5. Lee K, Anastasopoulou C, Chandran C, et al. Thyroid Cancer. [Updated 2021 Jul 19]. In: StatPearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459299/
6. Roman BR, Morris LG, Davies L. The thyroid cancer epidemic, 2017 perspective. Current opinion in endocrinology, diabetes, and obesity. 2017 Oct;24(5):332.
7. Olson E, Wintheiser G, Wolfe KM, Droessler J, Silberstein PT. Epidemiology of thyroid cancer: a review of the National Cancer Database, 2000-2013. Cureus. 2019 Feb 24;11(2).
8. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016 Jan 1;26(1):1-33.
9. Medas F, Canu GL, Boi F, Lai ML, Erdas E, Calò PG. Predictive factors of recurrence in patients with differentiated thyroid carcinoma: a retrospective analysis on 579 patients. Cancers. 2019 Aug 22;11(9):1230.
10. Agate L, Lorusso L, Elisei R. New and old knowledge on differentiated thyroid cancer epidemiology and risk factors. Journal of endocrinological investigation. 2012 Jan 1;35(6 Suppl):3-9.
11. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in thyroid cancer incidence and mortality in the United States, 1974-2013. Jama. 2017 Apr 4;317(13):1338-48.
12. Alauddin M, Joarder AH. Management of thyroid carcinoma-an experience in Bangladesh. Indian Journal of Otolaryngology and Head and Neck Surgery. 2004 Jul;56:201-5.
13. Aziz A, Masood MQ, Sattar S, Fatima S, Islam N. Follicular thyroid carcinoma in a developing country: A 10-year retrospective study. Cureus. 2021 Jul 23;13(7).
14. McHenry CR, Phitayakorn R. Follicular adenoma and carcinoma of the thyroid gland. The oncologist. 2011 May;16(5):585-93.
15. Debashish Chanda. On the road to new salt legislation in Bagladesh: Honouring Iodized Salt Procedures. Portfolio Lead, GAIN Bangladesh, 2 Sep 2018.
16. Iodized Salt Bill Passed in the Parliament. Daily Bangladesh14 June 2021
17. Ylli D, Burman KD, Van Nostrand D, Wartofsky L. Eliminating the age cutoff in staging of differentiated thyroid cancer: the safest road?. The Journal of Clinical Endocrinology & Metabolism. 2018 May;103(5):1813-7.
18. Jonklaas J, Nogueras-Gonzalez G, Munsell M, Litofsky D, Ain KB, Bigos ST, Brierley JD, Cooper DS, Haugen BR, Ladenson PW, Magner J. The impact of age and gender on papillary thyroid cancer survival. The Journal of Clinical Endocrinology & Metabolism. 2012 Jun 1;97(6):E878-87.
19. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid. 2014 Jan 1;24(1):27-34.
20. Orosco RK, Hussain T, Brumund KT, Oh DK, Chang DC, Bouvet M. Analysis of age and disease status as predictors of thyroid cancer-specific mortality using the Surveillance, Epidemiology, and End Results database. Thyroid. 2015 Jan 1;25(1):125-32.
21. Nilubol N, Zhang L, Kebebew E. Multivariate analysis of the relationship between male sex, disease-specific survival, and features of tumor aggressiveness in thyroid cancer of follicular cell origin. Thyroid. 2013 Jun 1;23(6):695-702.
22. Liu FH, Kuo SF, Hsueh C, Chao TC, Lin JD. Postoperative recurrence of papillary thyroid carcinoma with lymph node metastasis. Journal of surgical oncology. 2015 Aug;112(2):149-54.
23. Park J, Kim K, Lim DJ, Bae JS, Kim JS. Male sex is not an independent risk factor for recurrence of differentiated thyroid cancer: A propensity score-matching study. Scientific Reports. 2021 Jul 21;11(1):14908.
24. Pujol PA, Daures JP, Nsakala NI, Baldet LI, Bringer JA, Jaffiol CL. Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. The Journal of Clinical Endocrinology & Metabolism. 1996 Dec 1;81(12):4318-23.
25. Shokoohi A, Berthelet E, Gill S, Prisman E, Sexsmith G, Tran E, White A, Wiseman SM, Wu J, Ho C. Treatment for recurrent differentiated thyroid cancer: a Canadian population based experience. Cureus. 2020 Feb 27;12(2).
26. Barres B, Kelly A, Kwiatkowski F, Batisse-Lignier M, Fouilhoux G, Aubert B, Dutheil F, Tauveron I, Cachin F, Maqdasy S. Stimulated thyroglobulin and thyroglobulin reduction index predict excellent response in differentiated thyroid cancers. The Journal of Clinical Endocrinology & Metabolism. 2019 Aug;104(8):3462-72.
27. Piccardo A, Arecco F, Puntoni M, Foppiani L, Cabria M, Corvisieri S, Arlandini A, Altrinetti V, Bandelloni R, Orlandi F. Focus on high-risk DTC patients: high postoperative serum thyroglobulin level is a strong predictor of disease persistence and is associated to progression-free survival and overall survival. Clinical nuclear medicine. 2013 Jan 1;38(1):18-24.
28. Polachek A, Hirsch D, Tzvetov G, Grozinsky-Glasberg S, Slutski I, Singer J, Weinstein R, Shimon I, Benbassat CA. Prognostic value of post-thyroidectomy thyroglobulin levels in patients with differentiated thyroid cancer. Journal of endocrinological investigation. 2011 Dec;34:855-60.
29. Liu L, Zhang X, Tian T, Huang R, Liu B. Prognostic value of pre-ablation stimulated thyroglobulin in children and adolescents with differentiated thyroid cancer. Thyroid. 2020 Jul 1;30(7):1017-24.
30. Couto JS, Almeida MF, Trindade VC, Marone MM, Scalissi NM, Cury AN, Ferraz C, Padovani RP. A cutoff thyroglobulin value suggestive of distant metastases in differentiated thyroid cancer patients. Brazilian Journal of Medical and Biological Research. 2020 Oct 9;53.
31. Ng SC, Kuo SF, Chen ST, Hsueh C, Huang BY, Lin JD. Therapeutic outcomes of patients with multifocal papillary thyroid microcarcinomas and larger tumors. International journal of endocrinology. 2017 Oct;2017.
32. Jo K, Lim DJ. Clinical implications of anti-thyroglobulin antibody measurement before surgery in thyroid cancer. The Korean journal of internal medicine. 2018 Nov;33(6):1050.
33. Lee SY, Rhee CM, Leung AM, Braverman LE, Brent GA, Pearce EN. A review: radiographic iodinated contrast media-induced thyroid dysfunction. The Journal of Clinical Endocrinology & Metabolism. 2015 Feb 1;100(2):376-83.
34. Spencer CA. Clinical utility of thyroglobulin antibody (TgAb) measurements for patients with differentiated thyroid cancers (DTC). The Journal of Clinical Endocrinology & Metabolism. 2011 Dec 1;96(12):3615-27.
35. Xie X, Hui T, Luo Y, Li H, Li G, Wang Z. Research on the properties of low temperature and anti-UV of asphalt with nano-ZnO/nano-TiO2/copolymer SBS composite modified in high-altitude areas. Advances in Materials Science and Engineering. 2020 Apr 30;2020:1-5.
36. Turanli S, Mersin HH. Serum antithyroglobulin antibody levels are not a good predictive factor on detection of disease activity in patients with papillary thyroid carcinoma. Journal of Cancer Research and Therapeutics. 2020 Apr 1;16(3):624-9