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

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INTRODUCTION

The reported incidence of hyperthyroidism (HT) in cross-sectional case series from Bangladesh is around 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 decades 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 as shown in table-1, a higher number of females ended 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 outcomes among 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.
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, the euthyroid outcome was found to be associated with a higher mean of dose-1 \((p = 0.007, \text{ Table 3})\). Further analysis revealed a significantly higher mean of dose-1 in female gender who ended up as euthyroid \((p = 0.005, \text{ Table 4})\).

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 \((p = 0.02, \text{ Table-6})\).
Outcome of repeated RAIT in hyperthyroidism

Figure 3: Distribution of biochemical outcomes among diagnostic categories

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

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

Doses’ profile and analysis of Dose-1

The administered radioactivity rose for subsequent 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-1 for each biochemical outcome categories were compared among patients grouped on the basis of administered dose instances of RAIT (Table 8). The mean of dose-1 was 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 (Figure 4). 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.

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 |
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 hypothyroid outcome 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 hypothyreosis which 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 series while 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 instances may 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 MNG in this series, received an apparently higher mean of dose -1 albeit with apparently less steep increment of doses in comparison to GD and STN, that ended up with a 65% of euthyroidism. 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 euthyroidism 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 practice with adherence to an institutional management-guideline that later has evolved 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.

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