Risk Factors Associated with Repeat Radioactive Iodine Therapy for Differentiated Thyroid Cancer in a Tertiary Care Center in the Philippines: A Retrospective Cohort Study

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Abstract

Introduction: Thyroid carcinoma remains the most common endocrine malignancy and incidence has increased due to improved diagnosis. Most Differentiated Thyroid Cancers (DTC) are indolent and easily cured with surgery, radioactive iodine (RAI) therapy and TSH suppression. However, persistent and recurrent disease is not uncommon among Filipinos. RAI therapy is being used more frequently even for low risk patients due to this observed aggressiveness of DTC in our population. This study sought to identify factors that are associated with failure of initial RAI for DTC, leading to repeat doses.

Methods: This is a single-center, retrospective cohort study conducted in the Nuclear Medicine Department of a tertiary care center in the Philippines, involving 325 patients who underwent RAI from 2006-2016

Results: Out of 570 patients who underwent RAI therapy for DTC, only 325 were included. Majority (n=280, 86%) had PTC and the rest had FTC (n=45, 14%). Twenty four percent (n=67) of the PTC group and 31% (n=14) of the FTC had subsequent RAI therapy after initial therapy due to either persistent or recurrent disease, with a mean interval of 21-22 months. Distant metastasis at presentation (M1), uptake in distant tissues on the initial post-therapy whole body scan (WBS) and TNM stage 4 were predictive for repeat RAI for FTC. A negative post-therapy WBS was found to be associated with no need for repeat RAI. On the other hand, the initial RAI dose of 150 mCi or higher was noted to be associated with repetition of RAI for PTC. Other risk factors noted were the presence of lymph nodes and distant metastasis at presentation and loco-regional uptake on the post-therapy WBS. Conversely, a negative post-treatment scan appeared to be protective against repeat RAI, as in FTC. However, multivariate analysis of risk factors showed that only metastasis at presentation (LN or distant) was associated with repeat RAI therapy.

Conclusion: The only risk factor associated with failure of initial RAI for patients with PTC and FTC in this study was distant metastasis at presentation. Nodal involvement at presentation was noted to be a significant factor for among those with PTC.

Keywords: papillary thyroid cancer, follicular thyroid cancer, recurrence, RAI

Introduction

Thyroid cancer is the most common malignancy of the endocrine system. Its incidence has increased over the recent years due to increased detection and improved diagnosis through utilization of neck ultrasonography that detects small tumors or subclinical disease, and fine-needle aspiration biopsy.[1] The true rise in incidence can be due to greater exposure to environmental carcinogens such as radiation from computed tomography scanning.[1,2] Differentiated thyroid cancer (DTC), either papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC), account for 90% of cases. It is usually an indolent disease and with adequate treatment consisting of surgery, radioactive iodine therapy (RAI) and long-term suppression of thyroid stimulating hormone (TSH) with levothyroxine, the prognosis is excellent, with an expected 10-year survival rate of 80-95%.[3-5]

Nevertheless, recurrence of disease is not uncommon and may lead to significant morbidity and poor quality of life. Filipinos in particular have been reported to be the ethnic group with the highest incidence of thyroid cancer in several studies.[6-8] DTC among Filipinos were found to be more aggressive, with reported higher mortality rates compared to non-Filipino Asians and non-Hispanic Whites of similar age.[9] Lo et al. retrospectively reviewed 723 Filipino patients with DTC and found the following risk factors to be significantly associated with recurrence: age >45 years, tumor size >4cm, multifocal and bilateral involvement of cancer, incomplete surgery, nodal involvement and distant metastases at presentation. Recurrence rates in their study were 32.9% for PTC and 29.1% for FTC. They found that RAI therapy was protective against recurrence for both types of DTC.[10] With adjuvant RAI, the likelihood of recurrence and

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death in high-risk patients is reduced but the benefit for lower risk patients is less clear.[11-13] The American Thyroid Association (ATA) currently recommends its use only for intermediate-risk and high-risk DTC, emphasizing careful selection of patients and the avoidance of overtreatment. However, in a local study of patients categorized as low-risk PTC by ATA criteria, recurrence nevertheless developed in up to 35.17% even in those who received remnant ablation, which was supposed to be protective.[14] Recurrence undoubtedly leads to greater treatment costs and additional risks with repeated exposure to radiation. This is likely the reason for the apparent routine utilization of RAI therapy among clinicians regardless of risk profile and with much higher doses than what is recommended by foreign guidelines. This study sought to characterize DTC patients in our locality and the factors associated with the need to repeat RAI. The identification of these factors would hopefully contribute to the formulation of local treatment and monitoring guidelines specifically tailored to our population.

Methods

This is a single-center retrospective cohort study conducted in a 660-bed capacity, private, tertiary care hospital in Cebu City, Philippines

The study included all patients aged 18 years and above who were referred for RAI therapy whether for remnant ablation after thyroid surgery or as adjuvant therapy for metastatic disease, from 2006-2016. Only those with the final histopathology indicating a well-differentiated type of thyroid cancer (PTC or FTC) were included. On the other hand, patients who underwent a lobectomy or subtotal thyroidectomy only were excluded, as well as those with incomplete or lacking data.

Records of patients who underwent RAI therapy were retrieved from the hospital information system and pathology department logbooks. Patient characteristics including age, sex and tumor characteristics, type of surgery performed, initial RAI dose and pre-ablative TSH levels, histopathology report, thyroglobulin (Tg) and TSH levels and metascans were noted. This is a retrospective study that used purposive sampling that included all patients in the specified census period.

Patients were separated into two groups: those who had a single dose of RAI and those who were referred back for a second or repeat dose. The mean was computed for the quantitative variables and proportion for the categorical variables. The groups were compared using a chi-square and independent t-test. Multivariate logistic regression analyses were used to determine significant factors associated with repeat RAI. The predictive power of each variable was calculated and expressed using odds ratio, 95% confidence interval (CI), and *p*-values (with 95% power). IBM SPSS ver 21 software was used.

This study was reviewed and approved by the Institutional Review Board of our institution. No further intervention or manipulation of the study subjects were done.

Operational definition of terms

1. Differentiated Thyroid Cancer–refers to malignancy of the thyroid follicular cells with the histopathologic features of either Papillary (PTC) or Follicular thyroid cancer (FTC)
2. High dose RAI–radioactive iodine therapy using ^{131}Iodine administered to a patient either for destruction of residual thyroid tissue after surgery (remnant ablation) or as adjuvant therapy for extra-thyroidal/metastatic disease, at a dose equal to or greater than 30 millicurie (mCi)
3. Recurrence–reappearance of disease more than one year after ablation, after the patient has been rendered disease-free (no evidence of disease); reported if one of the following is fulfilled:
   a. Elevated stimulated Tg level >2 ng/mL or unstimulated Tg >1 ng/mL with or without anti-Tg levels
   b. Recurrent or new neck lesions or distant metastases noted on imaging (ultrasound, SPECT/CT or WBS), proven by biopsy to be thyroid cancer or together with elevated Tg levels (in the absence of biopsy)
   c. Negative imaging but with elevated or rising Tg levels with or without anti-Tg levels
4. Persistent disease–reported if regional or distant metastases are detected on the initial post-therapy WBS or detected by other imaging methods within one year of ablation

Results

A total of 570 patients who underwent high dose RAI for DTC in our institution were reviewed; of these only 325 had complete data and hence, were included in the analysis. Of these 280 or 85% had PTC and the rest had FTC (n=45, 14%). The rest of the patient and tumor characteristics are shown below in Table I.

Table II and III both shows the patient and tumor characteristics of patients with FTC and PTC, respectively, grouped according to the number of RAI therapies received. The mean thyroglobulin level for patients with FTC at the time of repeat RAI was 125 ng/mL. The lowest value noted was 22.5 ng/mL and the highest was 6,400 ng/mL. The mean interval between the first dose of RAI and the repeat dose was 23 months.

Apart from bilateral tumor involvement, which was observed more in those who received a second dose, patient and other tumor characteristics were not significantly

Table I. Characteristics of patients with DTC who were given post-operative RAI categorized into papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC)

	Papillary n=280	Follicular n=45
Age (years, SD)	42.3 + 12.9	46.9 ± 12.1
Sex (%) Male Female	 53 (18.9) 227 (81.1)	 17 (37.8) 28 (62.2)
Tumor size (cm, SD)	2.0 ± 1.4	4.3 ± 2.1
Metastasis at presentation (%) Lymph nodes Distant	 122 (43.6) 7 (2.5)	 2 (4.4) 11 (24.4)
Multifocality of tumor (%) Yes No	 72 (25.7) 208 (74.3)	 5 (11.1) 40 (88.9)
Bilateral involvement (%) Yes No	 58 (20.7) 222 (79.3)	 1 (2.2) 44 (97.8)
Type of surgery (%) Complete Incomplete	 280 (100) 0	 45 (100) 0
Initial RAI dose (mCi, SD)	146.6 ± 24.5	157.6 ± 25.9
Pre-RAI TSH level	62.9 ± 36.2	52.7 ± 29.0
Interval between surgery and first RAI (mo, SD)	3.6 ± 12.8	5.1 ± 15.8
Post-therapy WBS (%) Thyroid residuals Regional metastases Distant metastases	 216 (77.1) 62 (22.1) 8 (2.9)	 29 (64.4) 9 (20.0) 11 (24.4)

Table II. Characteristics of patients with FTC who received one or more doses of RAI

Characteristics	Follicular thyroid cancer			
	All n=45	With repeat RAI n=14	Single dose of RAI n=31	
Age (years, SD)	46.9 ± 12.1	51.2 ± 8.1	44.9 ± 13.1	t=1.971; *p*=0.056
Sex (%) Male Female	 17 (37.8) 28 (62.2)	 4 (28.6) 10 (71.4)	 13 (41.9) 18 (58.1)	X^2=0.733; *p*=0.392
Tumor size (cm, mean)	4.3 ± 2.1	4.4 ± 2.3	4.2 ± 2.1	t=0.311; *p*=0.757
Initial RAI dose (mCi, SD)	157.6 ± 25.9	175.0 ± 24.0	149.7 ± 23.0	t=3.375; *p*=0.002
Interval (mos, SD)	5.1 ± 15.8	9.1 ± 25.1	3.3 ± 8.6	t=0.842; *p*=0.260
Pre-RAI TSH (uIU/ml, SD)	52.7 ± 29.0	43.6 ± 39.1	56.8 ± 26.4	t=1.329, *p*=0.191
Minimally invasive variant (%)	39 (86.7)	10 (71.4)	29 (93.5)	X^2=4.084; *p*=0.043
Widely invasive variant histology (%)	6 (13.3)	4 (28.6)	2 (6.5)	X^2=4.084; *p*=0.043
Multifocal (%)	5 (11.1)	3 (21.4)	2 (6.5)	X^2=2.190; *p*=0.139
Bilateral (%)	1 (2.2)	0	1 (3.2)	X^2=0.462; *p*=0.497
Metastasis at presentation (%) Lymph nodes Distant mets	 2 (4.4) 11 (24.4)	 1 (7.1) 10 (71.4)	 1 (3.2) 1 (3.2)	 X^2=0.348; *p*=0.555 X^2=24.290; *p*=0.000
Post-therapy WBS (%) Negative Regional mets Distant mets	 29 (64.4) 9 (20.) 11 (24.4)	 4 (28.6) 3 (21.4) 8 (57.1)	 25 (80.6) 6 (19.4) 3 (9.7)	 X^2=24.290; *p*=0.000 X^2=0.026; *p*=0.872 X^2=11.765; *p*=0.001
TNM staging Stage I Stage II Stage III Stage IV	 17 (37.8) 5 (11.1) 11 (24.4) 12 (26.7)	 2 (14.3) 0 2 (14.3) 10 (71.4)	 15 (48.4) 5 (16.1) 9 (29.0) 2 (6.5)	 X^2=21.354, *p*=0.000

Table III. Characteristics of patients with PTC who received one or more doses of RAI

Characteristics	Papillary thyroid cancer			
	All n=280	With repeat RAI n=67	Single dose of RAI n=213	
Age (years, mean)	42.3 ± 12.9	42.0 ± 13.7	42.4 ± 12.7	t=0.232; *p*=0.817
Sex (%) Male Female	 53 (18.9) 227 (81.1)	 16 (23.9) 51 (76.1)	 37 (17.4) 176 (82.6)	X^2=1.407; *p*=0.235
Tumor size (cm, SD)	2. ± 1.4	2.1 ± 1.1	2.6 ± 1.5	t=2.616; *p*=0.009
Initial RAI dose (mCi, SD)	146.6 ± 24.5	154.3 ± 22.4	144.2 ± 24.7	t=2.955; *p*=0.003
Interval between surgery and ablation (mos, SD)	3.6 ± 12.8	16.0 ± 1.9	11.7 ± 0.8	t=0.237; *p*=0.813
TSH pre-ablation (ulu/ml, SD)	62.9 ± 36.2	71.5 ± 54.3	60.3 ± 27.8	t=1.623; *p*=0.109
Histologic variant (%) Classic Oncocytic Follicular	 196 (70.0) 1 (0.4) 82 (29.3)	 45 (67.2) 0 22 (32.8)	 151 (70.9) 1 (0.5) 60 (28.2)	 X^2=0.337; *p*=0.561 X^2=0.316; *p*=0.574 X^2=0.536; *p*=0.464
Multifocal (%)	72 (25.7)	19 (28.4)	53 (24.9)	X^2=0.322; *p*=0.570
Bilateral involvement (%)	63 (22.5)	23 (34.3)	40 (18.8)	X^2=7.067; *p*=0.008
Metastasis at presentation (%) Lymph nodes Distant Metastasis	 122 (43.6) 7 (2.5)	 49 (73.1) 5 (7.5)	 73 (34.3) 2 (0.9)	 X^2=31.307; *p*=0.000 X^2=8.899; *p*=0.003
Post-therapy WBS (%) Negative Regional metastasis Distant metastasis	 216 (77.1) 62 (22.1) 8 (2.9)	 43 (64.2) 23 (34.3) 3 (4.5)	 173 (81.2) 39 (18.3) 5 (2.3)	 X^2=8.395; *p*=0.004 X^2=7.586; *p*=0.006 X^2=0.752; *p*=0.386
TNM staging (%) Stage I Stage II Stage III Stage IV	 192 (68.6) 39 (13.9) 17 (6.1) 32 (11.4)	 46 (68.7) 5 (7.5) 3 (4.5) 13 (19.4)	 146 (68.5) 34 (16.0) 14 (6.6) 19 (8.9)	 X^2=7.913; p=0.048

Table IV. Bivariate logistic regression analysis of factors for repeat RAI on FTC

Characteristics	Follicular thyroid cancer			
	Repeat RAI n=14(%)	Single dose of RAI n=31(%)	O.R.	*p*-value
Age, >45 years	10 (71.4)	16 (51.6)	2.344	0.219
Sex, Male	4 (28.6)	13 (41.9)	0.554	0.395
Tumor size, >4 cm	7 (50.0)	15 (48.4)	1.067	0.920
Interval between surgery and ablation, >3 mos	4 (28.6)	5 (16.1)	2.080	0.340
Initial RAI dose, >150 mCi	14 (100.0)	24 (77.4)	9.424E10	0.999
Tg level, >2 ng/ml	12 (85.7)	0	0.542	0.014
Pre-RAI TSH, >30 uIU/ml	9 (64.3)	23 (74.2)	0.626	0.499
Widely invasive variant	4 (28.6)	2 (6.5)	05.800	0.062
Multifocal	3 (21.4)	2 (6.5)	3.955	0.160
Bilateral involvement	0	1 (3.2)	0.000	1.000
TNM stage I (reference) II III IV	 2 (14.3) 0 2 (14.3) 10 (71.4)	 15 (48.4) 5 (16.1) 9 (29.0) 2 (6.5)	 - 0.000 1.667 37.500	 - 0.999 0.638 0.001
Lymph node at presentation (N1)	1 (7.1)	1 (3.2)	2.308	0.565
Distant metastasis (M1)	10 (71.4)	1 (3.2)	75.000	0.000
Post-treatment WBS Negative/Residuals only Region metastasis Distant metastasis	 4 (28.6) 3 (21.4) 8 (57.1)	 25 (80.6) 6 (19.4) 3 (9.7)	 0.096 1.136 12.444	 0.002 0.872 0.002

Table V. Bivariate logistic regression analysis of factors for repeat RAI on PTC

Characteristics	Papillary thyroid cancer			
	Repeat RAI n=67 (%)	Single dose of RAI n=213 (%)	O.R.	*p*-value
Age, >45 years	24 (35.8)	82 (38.9)	0.878	0.655
Sex, Male	16 (23.9)	37 (17.4)	1.492	0.237
Tumor size, >4 cm	5 (7.5)	35 (16.5)	0.048	0.073
Initial RAI dose, >150 mCi	58 (86.6)	149 (70.0)	2.768	0.009
Tg level, >2 ng/mL	66 (98.5)	0	0.315	0.000
Pre-RAI TSH, >30 uIU/ml	57 (85.1)	182 (85.4)	0.971	0.940
Interval between surgery and ablation, >3 mos	9 (13.4)	32 (15.0)	0.878	0.748
Histologic variant				
Classic	45 (67.2)	151 (70.9)	0.840	0.562
Oncocytic	0	1 (0.5)	0.000	1.000
Follicular	22 (32.8)	60 (28.2)	1.247	0.465
Multifocal	19 (28.4)	53 (24.9)	1.318	0.375
Bilateral involvement	23 (34.3)	40 (18.8)	1.589	0.156
Lymph node metastasis at presentation, N1	49 (73.1)	73 (34.3)	5.221	0.000
Distant metastasis at presentation, M1	5 (7.5)	2 (0.9)	8.508	0.012
TNM staging				
I (reference)	46 (68.7)	146 (68.5)	-	-
II	5 (7.5)	34 (16.0)	0.467	0.134
III	3 (4.5)	14 (6.6)	0.680	0.558
IV	13 (19.4)	19 (8.9)	2.172	0.051
Post-therapy WBS				
Negative/Residuals only	43 (64.2)	173 (81.2)	0.414	0.004
Regional metastasis	23 (34.3)	39 (18.3)	2.332	0.007
Distant metastasis	3 (4.5)	5 (2.3)	1.950	0.369

Table VI. Multivariate logistic regression analysis on repeat RAI for FTC and PTC

Characteristics	Odds ratio	95% C.I.	*p*-value
RAI for FTC			
Presence of Distant Mets	75.000	7.480-751.975	0.000
RAI for PTC			
Presence of LN Mets	5.899	3.104-11.213	0.000
Presence of Distant Mets	10.800	1.556-74.973	0.016

different between the two groups. (Table III) As in FTC, the PTC group who received additional RAI therapy received higher initial doses of RAI (154 vs 144) and had nodal or distant metastases at presentation, indicating a higher baseline risk.

A bivariate analysis of all factors was done to determine predictors of repeat RAI therapy for patients with FTC. (Table IV) Similar to the ATA risk stratification system, an elevated stimulated thyroglobulin level >2ng/mL, distant metastasis and TNM Stage 4 at presentation and persistent uptake in distant tissues on the post-therapy WBS were significant prognostic factors for a repeat RAI therapy after surgery and initial RAI for remnant ablation and adjuvant therapy. In contrast, a negative uptake outside of the thyroid bed on the post-therapy WBC was predictive of a single dose of RAI.

The same bivariate analysis was done on the significant factors for PTC revealed that an initial RAI dose of equal to or more than 150 mCi was predictive of the need for a repeat dose. Similar to FTC, a post-therapy WBS showing only thyroid residuals and no uptake elsewhere was a predictive factor for the likely success of the initial RAI. (Table V)

When all the significant factors were included in the model for the multivariate analysis, the presence of distant metastasis at presentation was the only significant prognostic factor for the repetition of RAI for FTC (Table VI). For PTC, both nodal and distant metastases were factors observed to be predictive for subsequent RAI (Table VI).

Discussion

Majority (86%) of patients included in this study who had PTC are females, with a mean age of 42.3 years at diagnosis and 46.9 years for FTC, consistent with the established propensity of this type of cancer to affect females between

30 and 50 years old.[15] In men, thyroid cancer tends to be more aggressive at diagnosis.[16] In our study however, male patients with either FTC or PTC did not demonstrate an increased risk for persistent or recurrent disease based on the need for repeated doses of RAI. The cut-off age of 45 years set by the American Joint Committee on Cancer TNM Classification was not found to be associated with repetition of RAI in our study, indicating no significant association of age with aggressive tumor behavior.[17] The same age cut off was also not shown to be predictive of the success or failure of initial RAI in the study of Liu, et al.[18]

Persistent or recurrent disease is the most common reason for the repetition of RAI therapy. To date, only a few local studies have looked into the risk factors for recurrence among Filipinos and the exact reason why DTC tends to be aggressive in our ethnicity remains to be investigated further with genetic studies. In addition to the many of the well-known risk factors for recurrence of DTC such as tumor size >4cm, aggressive histologic variant and metastasis at presentation, multifocality and bilaterality of tumor involvement, which were unique risk factors observed in the study of Lo TEN, et al., did not appear to be significant predictors for repeat RAI in our study.[10]

Even though the use of RAI has been demonstrated to reduce recurrence and mortality rate in DTC, there's still no consensus among guidelines about the optimal dose of 131Iodine for ablation.[10,18] In our institution, a fixed dose protocol is being employed. The mean RAI dose for initial therapy in our study is 146.6+24.5 and 157.6+25.9 mCi for PTC and FTC, respectively, much higher than the dose for ablation and adjuvant therapy recommended by the ATA.[17] The higher doses observed for those who were eventually subjected to a second round of RAI indirectly tells us that these patients had a higher risk profile at the outset. However, despite the relatively high activities used, the rate of repeat RAI, indirectly reflecting the rate of persistent/recurrent for PTC and FTC, is at 24% and 31%, respectively, again reflecting the aggressiveness of DTC among Filipino patients.

The clinical value of measuring pre-ablative Tg level has been reported in several studies, especially with regard to progression or recurrence of DTC. A value greater than 5 ng/mL was considered as the most powerful predictor for ablation failure.[18] Obtaining a Tg level prior to RAI therapy is not done routinely in our institution, as this test is too expensive for most patients. The unavailability of this test for some patients led to the exclusion of patients and a significant decrease in the sample size of this study.

What remains consistent across all local and international studies is the prognostic significance of the presence and location of metastasis of DTC. Nodal metastasis is observed in up to 79% of patients with PTC and less for FTC consistent with their primary mode of spread.[19] Lymph node metastases have been widely accepted as a risk factor for recurrence of PTC, but its influence on survival is unclear.[20] In this study, patients who had lymph node metastasis at presentation were at risk for subsequent RAI therapy in PTC (OR 5.899, *p*-0.000). The presence of distant metastasis, although rare, occurring only in about three percent of patients with DTC, is associated with increased risk of recurrence and death.[21] This study found that distant metastasis is the only consistent factor that predicts the need for subsequent RAI for either type of DTC (OR 75, *p*-0.000 and OR 10.800, *p*-0.016, respectively).

Conclusion

In this study, the presence of distant metastasis at presentation and on initial post-therapy WBS was associated with an increased risk for repeat RAI for patients with PTC or FTC.

This study has several limitations. First, the data retrieval is retrospective in nature; hence, information is limited to what was written on the patient's charts. Histopathology reports were variable, being reported by different pathologists from different referring institutions. Patients from other hospitals lack a detailed biopsy report, and results of meta-scans and other relevant imaging were difficult to retrieve, if not impossible. Furthermore, many charts were excluded from the analysis due to lack of Tg, TSH and anti-Tg values. In addition, the retrospective design of this study prevented further analysis of factors related to the outcome. Hence, a prospective trial on the subject including a subgroup analysis on patients who were low risk by ATA criteria but still needed a second RAI therapy is recommended.

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