Relationship between first radioactive iodine administration time and initial response to treatment in patients with papillary thyroid carcinoma

Original Article

Tahereh Ghaedian[1], Mohammad Ramezani[1], Hamideh Sadra[1], Marjan Faghih[2]

[1]Nuclear Medicine and Molecular Imaging Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Biostatistics, Faculty of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

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ABSTRACT

Introduction: The initial post-surgical radioactive iodine (RAI) therapy for patients with papillary thyroid cancer (PTC) is postponed due to increased demand as well as the limited number of centers to provide RAI therapy. Hence, our aim was to investigate the role of first RAI administration time following thyroidectomy on the number of incomplete response (IR) during the initial follow up, while considering other prognostic factors.

Methods: Two hundred and thirty-five PTC patients who were admitted to our department for RAI therapy were included in this study. They were allocated into two groups with <3 months (early group) and ≥ 3 months (delayed group) time interval after the first RAI therapy, and the total thyroidectomy. Then, based on the response to RAI therapy, patients were categorized as excellent, biochemical incomplete, structural incomplete, or indeterminate responses (ER, BIR, SIR or IDR, respectively).

Results: With respect to age, gender, pathologic variables, RAI dose rate and IR (BIR+SIR) rate, significant differences were found between the two groups. The findings identified that early RAI failed to affect the rate of IR (univariate analysis: HR=1.09, 95%CI: 0.69-1.74, P=0.71; Cox model: HR=0.81, 95%CI: 0.46-1.44, P=0.47). However, Cox multivariate analysis found lymph node status and thyroglobulin level (Lymph node status: HR=2.88, 95%CI: 1.07-7.78, P=0 .04) as independent risk factors for IR during the initial follow up.

Conclusion: Therefore, timing of the first post-surgery RAI therapy is not a significant prognosticator of the initial response of patients to therapy.

Key words: Papillary thyroid cancer; Radioactive iodine; Administration time; Response to therapy

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Corresponding author: Dr. Tahereh Ghaedian, Nuclear Medicine Department, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran. E-mail: tghaedian@gmail.com

INTRODUCTION

Papillary thyroid carcinoma is one of the most common type of malignancies (>80%), with almost triple increase in yearly incident over the past 30 years [1-3]. Total thyroidectomy followed by radioactive iodine (RAI) administration is well-established as the standard of care as ablative and therapeutic management for metastatic and non-metastatic tumors [4, 5]. In the past few decades, following the rise in the incidence of thyroid cancer (DTC) [6-8], demand has increased for RAI therapy, and this in addition to the limited numbers of medical facilities for RAI therapy [9] has resulted in a significant delay time between thyroidectomy and the initial RAI therapy [10]. Hence, there is a concern regarding the disease progression, which can be prevented by earlier administration of RAI. On the other hand, there are only few studies that have evaluated the impact of initial RAI therapy after thyroidectomy [1, 2, 11-13], and there is still much controversy with respect to the impact of postponed RAI therapy on the prognosis and the outcome. Therefore, the present study was designed to investigate the impact of time interval between the first RAI therapy and thyroidectomy on the rate of incomplete response (IR) during the initial follow up, while considering other prognostic factors.

METHODS

Patient population

This is a retrospective study on patients admitted to our department from June 2016 until August 2017 for RAI therapy due to papillary thyroid cancer. Since patients who receive 30 mCi RAI are not hospitalized and do not have a complete hospital history, we only included the patients who were scheduled to receive ≥100 mCi. Inclusion criteria are; 1) papillary thyroid carcinoma, 2) previous total or near-total thyroidectomy, 3) complete medical history with first follow up visit of at least 6 months' duration. Patients with high anti-thyroglobulin Ab level were excluded from thyroglobulin analysis.

Clinical data and RAI therapy

Records of all PTC patients were retrospectively evaluated for demographic and medical data. Histologic variant of PTC was categorized as aggressive types (tall cell, columnar cell and hobnail cells) and non-aggressive types (follicular and classic variant of PTC). Tumor size, presence or absence of lymphatic invasion, vascular invasion, extra-thyroid extension and lymph node involvement (if any LN was excised during surgery) were also extracted from the pathology reports. Stimulated serum thyroglobulin and anti-thyroglobulin level as well as serum TSH before RAI therapy were also recorded. Presence or absence of distant metastasis was assessed based on clinical and imaging (WBS) data.

Following the initial referral of the patients to our department, individuals were scheduled for RAI with dose of 100 to 200 mci, according to their baseline pathological features. Patients were asked to stop taking levothyroxine for 4 weeks before the RAI therapy and then continue it the day after. For all patients, WBS was performed 5-7 days after therapy. In our department, time interval between the thyroidectomy and the RAI therapy is generally depending on the waiting list and the time of patient's accessibility at the time. In addition, it should be noted that in our center, there is a slightly higher tendency to admit high-risk patients earlier. Hence, patients were categorized based on the time interval of their first RAI therapy and total thyroidectomy as <3 months (early group) and ≥ 3 months (delay group).

Follow up

In our department, at least one stimulated thyroglobulin and anti-thyroglobulin level are requested after the initial RAI therapy with the interval of at least 6 months to evaluate the response to therapy and the efficacy of ablation.

In the case of high or rising of the thyroglobulin level during the follow up, appropriate treatment measures were considered, and when thyroglobulin level was low or declining, WBS was performed to compare with post-therapy WBS. Assessment of therapy response was performed based on the American Thyroid Association guideline (4). Thus, the response is categorized based on the clinical, biochemical, imaging or cytopathology findings based on the first follow up after initial radioiodine therapy as; excellent, biochemical incomplete, structural incomplete, or indeterminate responses (ER, BIR, SIR or IDR, respectively).

Statistical analysis

The Pearson's chi-square test was used to check the relationship between gender, subtype, capsular invasion, extra-thyroidal extension, vascular invasion, lymphatic invasion, surgical margin involvement, multi-centricity, lymph node status, distant metastasis, ATA risk status and the rate of incomplete response (IR) with group membership. Independent t-test or Mann Whitney U test was used to examine the mean differences in age, size, radioiodine dose (mci), thyroglobulin (ng/dl), TSH, and anti-thyroglobulin Ab (ng/dl) between the two groups. We utilized Shapiro-Wilk test to assess normality and the Levene's test for homogeneity of variances. The univariate analysis was conducted by univariate cox regression for the influence of the initial RAI timing, age, gender, subtype, size, Capsular invasion, extra-thyroidal

extension, Vascular invasion, Lymphatic invasion, Surgical margin involvement, multi-centricity, Lymph node status, Distant metastasis, ATA risk status, Radioiodine dose, thyroglobulin, TSH, anti-thyroglobulin Ab, and time interval. Variables with significant or borderline significant values ($P \leq .10$) in the univariate analysis were entered into the Cox model for multiple analyses. All analyses were performed, using the SPSS statistical software, version 22. The $p<0.05$ was considered to be statistically significant.

RESULTS

Of the 235 patients, the average age at diagnosis was 38 (16-74) years. After median follow-up duration of 9 (4-25) months for the initial response evaluation, there were 131 (55.7%), 6 (2.6%), 80(34%) and 18(7.7%) patients with ER, BIR, SIR and IDR, respectively. Clinical and pathological characteristics of group 1 (n = 161) and 2 (n = 74) are summarized in Table 1. The 2 groups did not differ significantly with respect to age, gender, subtype, size, Capsular invasion, extra-thyroidal extension, Vascular invasion, Lymphatic invasion, Surgical margin involvement, multi-centricity, Lymph node status, Distant metastasis, ATA risk status, Radioiodine dose, thyroglobulin, TSH, anti-thyroglobulin Ab, time interval, and rate of IR (BIR+SIR) (Table 1).

Table 1: Baseline characteristics of all patients (Mean±SD or n (%)).

Variable		Total	<3 month (n=161)	>=3month (n=74)	p-value
Age (years)		39.99±12.98	40.03±12.26	39.92±14.5	0.95
Gender	Female	201(85.5)	135(84)	66(89.2)	0.28
	Male	34(14.5)	26(16)	8(10.8)	
Subtype	Non-aggressive	213(90.7)	146(90.7)	67(90.5)	0.97
	Aggressive	22(9.4)	15(9.3)	7(9.5)	
Size (cm)		2.31±1.62	2.2±1.56	2.55±1.73	0.14
Capsular invasion	No	158(67.5)	105(65.6)	53(71.6)	0.36
	Yes	76(32.5)	55(34.4)	21(28.4)	
Extra-thyroid extension	No	205(87.2)	145(90.1)	60(81.1)	0.06
	Yes	30(12.8)	16(9.9)	14(18.9)	
Vascular invasion	No	202(86)	138(85.7)	64(86.5)	0.87
	Yes	33(14)	23(14.3)	10(13.5)	
Lymphatic invasion	No	186(79.1)	125(77.6)	61(82.4)	0.4
	Yes	49(20.9)	36(22.4)	13(17.6)	
Surgical margin involvement	No	209(88.9)	142(88.2)	67(90.5)	0.59
	Yes	26(11.1)	19(11.8)	7(90.5)	
Multi-centricity	No	154(65.5)	103(64)	51(68.9)	0.46
	Yes	81(34.5)	58(36)	23(31.1)	
Lymph node status	Not submitted	145(61.7)	93(57.8)	52(20.3)	
	Positive	56(23.8)	42(26.1)	14(18.9)	0.19
	Negative	34(14.5)	26(16.1)	8(10.8)	
Distant metastasis	No	216(91.9)	146(90.7)	70(94.6)	0.31
	Yes	19(8.1)	15(9.3)	4(5.4)	
ATA risk status	Low	54(23)	38(23.6)	16(21.6)	
	Intermediate	121(51.5)	82(50.9)	39(52.7)	0.94
	High	60(25.5)	41(25.5)	19(25.7)	
Radioiodine dose (mCi)		131.59±1.68	132.29±2.05	130.07±2.93	0.55
Thyroglobulin (ng/dl)		28.5±6.32	36.41±9.09	11.75±3.57	0.19 *
Anti- thyroglobulin Ab(ng/dl)		200.39±55.18	216.83±73.61	164.89±72.14	0.66
TSH		75.35±3.29	77.77±3.62	69.99±6.87	0.27
Follow-up duration (months)		9.48±0.23	9.44±3.27	9.57±3.82	0.79
Rate of IR		86(37)	61(37.9)	25(35.1)	0.69

*Mann Whitney test

Table 2: Univariate and multiple Cox regression analysis.

Variable		Univariate			Multiple		
		Hazard Ratio (HR)	95%CI for HR	P-value	Hazard Ratio (HR)	95%CI for HR	P-value
Initial RAI timing	<3 month	1.09	0.69-1.74	0.710	0.81	0.46-1.44	0.47
	>=3month	1.00			1.00		
Age		1.00	0.99-1.02	0.910			
Gender	Female	1.00	1.48-4.03	P<0.001	1.00	0.99-3.32	0.53
	Male	2.45			1.82		
Subtype	Non-aggressive	0.84	0.40-1.75	0.640			
	Aggressive	1.00					
Size		1.08	0.96-1.22	0.190			
Capsular invasion	No	1.02	0.65-1.59	0.930			
	Yes	1.00					
Extra-thyroid extension	No	1.00	0.99-2.88	0.050	1.00	0.45-2.02	0.89
	Yes	1.69			0.95		
Vascular invasion	No	1.00	0.93-2.69	0.090	1	0.87-3.67	0.12
	Yes	1.59			1.78		
Lymphatic invasion	No	1.00	0.96-2.43	0.070	1.00	0.18-1.00	0.05
	Yes	1.53			0.43		
Surgical margin involvement	No	0.68	0.39-1.22	0.200			
	Yes	1.00					
Multi-centricity	No	0.93	0.60-1.43	0.740			
	Yes	1.00					
Lymph node status	Not submitted	1.03	0.54-1.96	0.930	1.10	0.51-2.39	0.80
	Positive	2.35	1.20-4.59	0.010	2.88	1.07-7.78	0.04
	Negative	1.00			1.00		
Distant metastasis	No	1.00	1.36-4.16	0.002	1.00	0.47-3.43	0.63
	Yes	2.38			1.28		
ATA risk status	Low	1.00			1.00		
	Intermediate	1.52	0.79-2.92	0.220	1.04	0.5-2.15	0.90
	High	3.01	1.58-5.75	0.001	1.22	0.49-3.02	0.67
Radioiodine dose		1.01	1.00-1.02	0.002	1.00	0.99-1.02	0.70
Thyroglobulin		1.00	1.001-1.004	P<0.001	1.00	1.001-1.006	0.01
Anti-thyroglobulin Ab		1.00	0.99-1.00	0.630			
TSH		1.00	1.00-1.008	0.060	1.00	0.99-1.007	0.27

In the univariate analysis, gender, presence of extra-thyroid extension, vascular invasion, lymph node status, lymphatic invasion, distant metastasis, high and intermediate ATA risk status, higher radioiodine dose, thyroglobulin and TSH level were considered as the risk factors for IR considering the significant level at 0.1($P \leq 0.1$) (Table 2). These variables were included in the multiple Cox regression analysis, which revealed that only lymph node status and thyroglobulin level were shown to be an independent risk factor for IR during the initial follow up (Lymph node status: HR=2.88, 95%CI: 1. 07-7.78, P=0.04, and for thyroglobulin: HR=1.003, 95%CI: 1-1.006, P=0.01). Lymphatic invasion showed to be a borderline significant risk factor for IR (P= 0.051), and other factors did not present prognostic value (Table 2).

Cox diagram for the initial RAI timing is shown in Figure 1 and hazard function of variables with significant relationship to IR by univariate cox analysis (P<0.05) are shown in Figure 2.

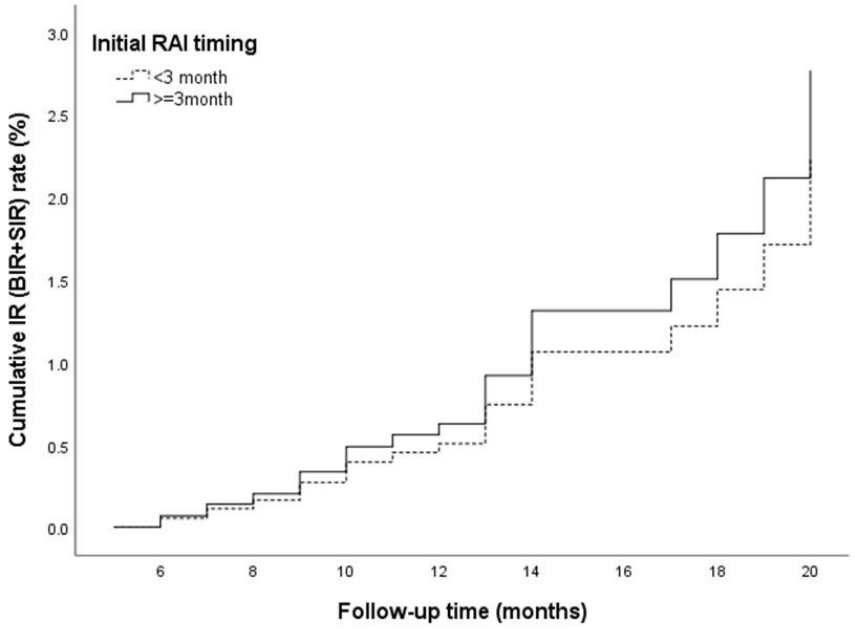

Fig 1. Cox hazard function for initial RAI timing < 3 months and ≥3 months in all patients (P= 0.47).

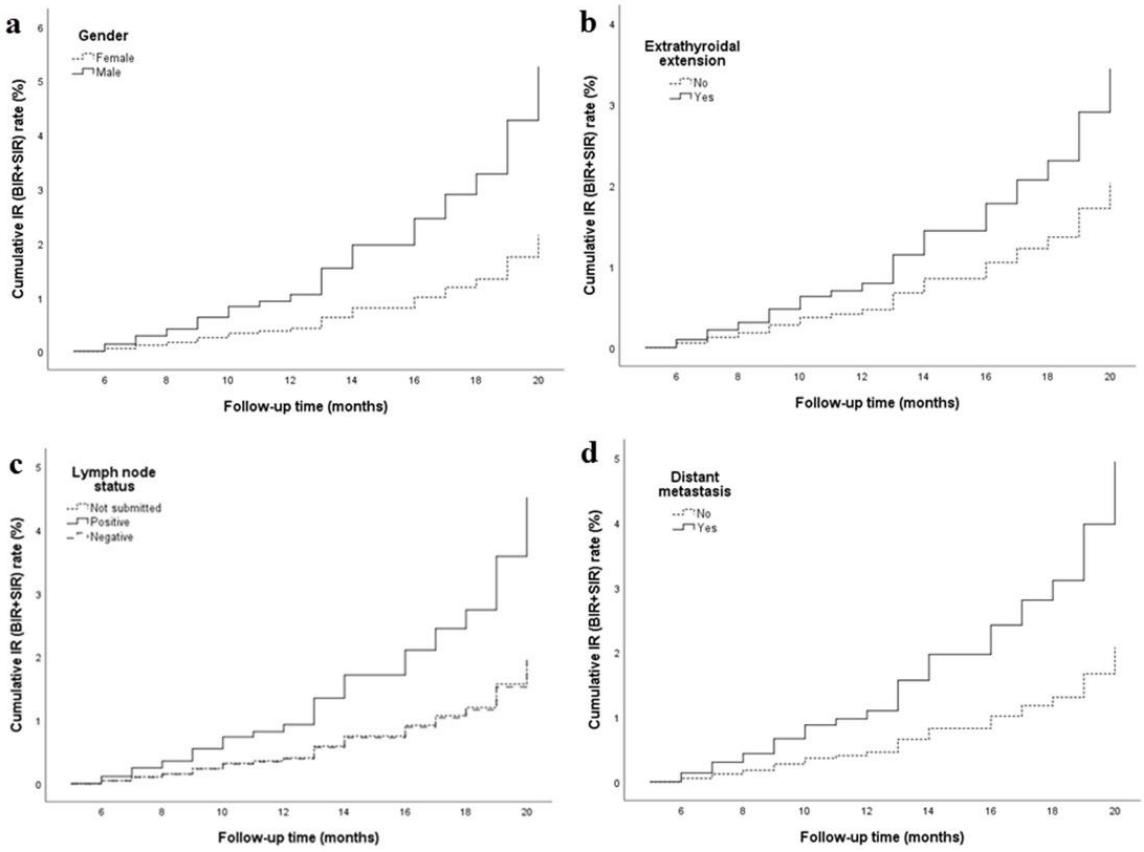

Fig 2. Hazard function of gender, extra thyroidal extension, lymph node status and distant metastasis (P<0.05 by univariate Cox regression analysis).

Table 3: Univariate Cox regression analysis for initial RAI timing (reference: >=3month) in ATA risk status subgroups.

Variable		Rate of IR	Hazard Ratio(HR)	95% CI for HR	P-value
ATA risk status	Low	12/54(22%)	1.63	0.43-6.15	0.47
	Intermediate	35/121 (29%)	0.59	0.29-1.21	0.15
	High	21/60 (35%)	1.73	0.84-3.56	0.14

Univariate Cox regression analysis in the subgroup of low, intermediate or high- risk patients showed no significant relationship between the initial RAI timing and rate of IR at initial follow up after therapy (Table 3).

DISCUSSION

This study suggest that patients treated with RAI for up to 3 months after total thyroidectomy exhibited no significant difference with respect to the rate of IR in comparison with those who received delayed treatment (≥3 months). Even in subgroups of patients with low, intermediate or high-risk features, based on ATA guideline, there was no significant relationship with time of RAI therapy and the rate of IR. However, our study revealed that positive lymph node metastasis confirmed by pathology is an independent predictor of IR during the initial follow up. Although, thyroglobulin level was significantly related to IR, it failed to meet a clinical significance giving the low HR (1.003).

The standard treatment of PTC is the excision of the primary tumor by surgery, followed by RAI therapy in cases with higher risk of persistent disease, and to ablate the thyroid remnant tissue for better follow up [14, 15]. While the most common rout of disease spread is *via* loco regional lymphatics, incomplete local therapy or ablation can increase the risk of local recurrence [16-18], and further therapies maybe indicated. Thus, RAI, as a well-stablished ablative treatment [19, 20] is widely performed after near-total or total thyroidectomy for patients with DTC. However, there is usually a concern for both patients and physician about the timing of RAI therapy following thyroidectomy to prevent local spread or growth before RAI can limit or ablate the remnant disease or thyroid tissue. Several studies evaluated the impact of initial RAI timing on the long-term outcome of DTC patients [1, 2, 11-13]. Since, there are some basic differences in the definition of early *vs.* delayed RAI therapy, follow up duration, initial risk of patients and the RAI dosing protocol, the direct comparison of studies in some cases can be misleading. Nonetheless, the majority of studies failed to detect any significant relationship between the initial RAI timing and patient's outcome. A study by Tsirona et al. revealed that timely initiation of RAI would not result in better remission rate in low-risk DTC [1]. Another study by Suman et al. on low and intermediate risk PTC patients also showed that delay in RAI therapy after surgery is not related adversely affecting the overall survival (OS) in these patients [2]. However, findings on high-risk patients are more controversial. In a study by Higashi et al. amongst high-risk metastatic patients, the OS rate of the metastatic DTC patients is significantly lower in patients with RAI therapy after 6 months post-surgery [12]. They also found that age, thyroglobulin level and extent of metastasis are the other independent factors related to OS amongst these patients. Our results are in contrast to Suman et al. study on high-risk patients. In this study, early RAI therapy after thyroidectomy was not independently related to OS [2]. All the mentioned studies evaluated the long-term prognostic role of the initial RAI timing. However, patients with PTC have generally a good long-term prognosis. Hence, considering the excellent prognosis of DTC, we decided to evaluate the short-term outcome of patients as the initial response to RAI therapy; thus, patients with IR are at higher risk of disease recurrence in the future.

A study by Scheffel et al. conducted on 545 patients, showed that delayed RAI therapy after thyroidectomy (>6 months) has no impact on both the initial response to therapy, which is defined as the rate of IR after 1 year of follow up, and rate of recurrence at longer follow up period (on average 6 years) [11]. Although they found no relationship between the outcome and initial timing of RAI therapy in each of the ATA risk groups, their sample merely included patients with a wide range of RAI dose (30-200 mCi). A study by Li et al. also evaluated the impact of initial RAI timing on the initial response of DTC patients based on recent ATA guideline [13]. They assessed 235 low and intermediate risk DTC patients and found that early RAI therapy (<3 months) after thyroidectomy is independently associated with higher rate of IR. In this study, patients received 30 (69%) or 100 (31%) mCi initial RAI therapy. However, in our study we included patients with initial RAI dose of ≥ 100 mCi, which includes low risk patients as well. By comparing our study with the Chinese group, the hypotheses might rise that RAI timing might be affected by the initial response when low RAI dose is administered. A more comprehensive study by another group from South Korea on 720 intermediate and

high-risk PTC patients revealed that delayed RAI therapy (mean 138 mCi), even up to 180 days had no significant impact on restaging, recurrence or mortality of patients with DTC [21]. The mean RAI dose in our patients was 131 mCi, and we also found that delayed initial RAI therapy was not associated with higher rate of IR. Krajewska et al. also compared the initial RAI within 9, 9-24 and >24 months after the initial diagnosis [22]. They also suggested that delayed initial RAI therapy >9 months after surgery was associated with poorer long-term outcome, but not in the intermediate or high-risk patients. In this study, low-risk patients were treated with lower doses of RAI (median RAI dose of 60 mCi).

Our study also suggested that the only independent predictive factor for IR during the initial follow up was the positive lymph node metastasis. This was also indicated by several previous studies.

CONCLUSION

Although the retrospective nature and relatively small sample of our study might have affected our findings, as combined with previous studies, it can be stated that initial RAI timing after thyroidectomy cannot be significantly related to the initial response of patients to the therapy. However, further prospective trials with larger sample size is still warranted to confidently conclude about the impact of initial RAI timing on the outcome of PTC patients; we also suggest further studies to separately evaluate the role of initial RAI timing in patients treated with low or high-dose RAI.

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