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Does Underlying Synchronous Benign Thyroid Tissue have an Effect on Radioactive Iodine Ablation Outcome in Papillary Thyroid Cancer?.

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ABSTRACT:

Objective: to explore the effect of the histopathological nature of the remnant thyroid tissue on the success of the ablation after the first dose of RAI-131. **Methods:** In this retrospective study, the clinical and pathological data of patients with histo-pathologically proven low to intermediate risk PTC were reviewed. The dose of RAI that was given to the patients ranged from 80 to 100 mCi. The clinical impact of the histopathology of the thyroid remnant was assessed by evaluating the ablation outcome at the post 6 months follow-up. Successful complete ablation was defined as structural and biochemical ablation as deduced from negative RAI-131 WBS and decrease in sTG level. Unsuccessful incomplete ablation was defined as the presence of persistent RAI-131 uptake in the thyroid bed, appearance of new RAI-131 uptake and/ or persistent high or rising sTG level. **Results:** Among a total of 130 patients, 33.8% had normal thyroid tissue remnant, 24.6% had Hashimoto's thyroiditis, 23.1% had MNG and 18.5% had colloid nodular goiter. Post-therapy scan was positive for thyroid residual and negative for loco-regional or distant metastases in all patients. Diagnostic post 6-months scan was positive in 29.2% (n= 38) of cases indicating incomplete ablation and was negative in 70.8% (n= 92) indicating complete ablation. The difference between complete and incomplete ablation in relation to the thyroid tissue background was statistically significant with a p-value of <0.001. Hashimoto's thyroiditis had a statistically significant different ablation outcome as compared to normal thyroid tissue, whereas the ablation outcome in the group of patients with MNG and colloid nodular goiter was not

statistically different when compared to normal thyroid tissue. There was a statistically significant difference in the ablation outcome between patients with autoimmune pathology and patients with non-auto-immune pathology with a p-value of p<0.001. As regards the baseline tumor markers, there was a statistically significant lower mean value of baseline stimulated anti-TG in patients with compete ablation (mean was 60.73) compared to patients with incomplete ablation (mean was 132.81) with a p-value of p=0.018, while the difference in stimulated TG value in the two groups was not statistically significant. Hashimoto's thyroiditis was a significant independent predicting factor for RAI-131 ablation outcome on univariate and multivariate regression analyses with a p-value= 0.002.

Conclusion: Individualization of RAI-131 ablation dose should take into consideration the nature of the thyroid tissue remnant. Patients with histopathological or laboratory evidence of auto-immune thyroiditis are recommended to receive a higher ablative dose to ensure a successful outcome.

Keywords: thyroid remnant ablation, Hashimoto thyroiditis, risk stratification of PTC

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INTRODUCTION:

The most prevalent kind of cancer of the thyroid is known as papillary thyroid cancer (PTC), which may develop in conjunction with benign thyroid diseases or against a backdrop of typical thyroid tissue [(1).] The best course of therapy for PTC is thought to include a complete or nearly total thyroidectomy, and then radiation-induced iodine I-131 (RAI-131) ablation of any remaining tissue from the thyroid (remnant ablation) [(2)]. "The degeneration of residual, macroscopically normal tissue of the thyroid after surgical thyroidectomy" is the definition of radioiodine ablation of thyroid remnants [(3)]. There are multiple persuasive rationales for residual ablation in PTC instances. Initially the RAI whole body scan (WBS) and tumor markers (TG and anti-TG) have difficulty identifying and treating nodal or distal metastases when there is leftover tissue from the thyroid present. Secondly, a large thyroid residual often precludes the high

amounts of thyroid-stimulating hormone (TSH) required to promote tumor I-131 absorption. Third, in the presence of typical tissue from the thyroid, the most sensitive technique for detecting recurrence—the measurement of blood thyroglobulin under TSH stimulation—is unreliable. Therefore, it is essential to ablate any remaining thyroid tissue since this makes follow-up easier [1]. Additionally, some researchers claim that remnant ablation may likely eliminate any concealed multifocal cancer that may return years later as well as any remaining follicular cells that might eventually become malignant, lowering the likelihood of tumor recurrence and perhaps even the death rate [4]. It has been observed that remnant ablation is an independent variable that lowers metastatic disease, cancer mortality, and loco-regional recurrence [5]. The precise histology of the non-neoplastic tissue of the thyroid, which makes up the majority, if not all, of the residual thyroid tissue left behind after surgery, is one of the factors that might influence a patient's reaction to RAI-131.

PATIENTS and METHODS:

This retrospective study comprised 130 individuals who went through a complete thyroidectomy for well-differentiated papillary cancer of the thyroid, as confirmed by histopathology, and who then presented to the Nuclear Medicine Department of Cairo University's Faculty of Medicine for follow-up and remnant ablation after surgery. The institutional research ethics commission approval was obtained. Data was collected from patients' records and all adult patients with PTC were included, irrespective of the histopathology of the extra-malignant background thyroid tissue (for which the histopathology revealed normal thyroid tissue or benign thyroid tissue pathology). Patients with partial thyroidectomy or lobectomy, patients with histopathology other than PTC, patients who were metastatic from the start (lymph nodes or distant metastases) and patients less than 18 years old were excluded from our study. All patients in our study belonged to the low to intermediate risk categories according to the revised American Thyroid Association Guidelines 2015 and accordingly, the RAI doses that were administered to the patients ranged from 80 to 100 mci. Cessation of levothyroxine therapy 4 weeks and consumption of low-iodine diet 2 weeks prior to dose administration were requested from the patients. Assessment of stimulated TSH

(s TSH), stimulated TG and stimulated Anti-TG was done few days before RAI dose administration. All patients had adequate CBC, renal functions prior to RAI-131 dose administration and had nothing per oral (NPO) for 4-6 hours prior to RAI-131 intake to ensure proper dose absorption [6]. Patients were treated according to our institutional protocol which is in line with American Thyroid Association Guidelines as follows: after the ablative RAI was administered, post-therapy WBS was performed 5 to 7 days. The first follow-up was done 6 months after the ablative dose administration by means of RAI WBS, neck ultrasound, stimulated TG (sTG) and stimulated anti-TG (s anti-TG). At the post 6 months assessment, successful complete ablation was defined as structural and biochemical ablation as deduced from RAI-131 WBS (no RAI-131 avid lesions neither in the neck nor elsewhere) and decrease in sTG level. Unsuccessful incomplete ablation was defined as the presence of persistent RAI-131 uptake in the thyroid bed, appearance of new RAI-131 uptake and/ or persistent high or rising sTG level. A large-field of view dual head SPECT-CT gamma camera equipped with a high-energies parallel-hole collimator was used to image the patients. A scanning speed of 6–8 cm/min was used in the continuous whole body capture mode. We utilized a twenty percent symmetric window with a center of 364 KeV. Following the collection of the whole-body picture, regional (spot) images were obtained for any place where aberrant RAI-131 uptake was seen or suspected on the whole-body images, as well as for the neck and chest regions, each for at least 200 K counts. When necessary, SPECT/CT was carried out on suspected regions of elevated uptake seen in the collected spot views or the planar whole body scan.

Statistical Analysis

The statistical software for the social sciences, or SPSS, version 28 (IBM Corp., Armonk, NY, USA) was used to code and input the data. For quantitative data, the mean, standard deviation, median, minimum, and maximum were used to summarize the data; for categorical data, the frequency (count) and relative frequency (%) were used. The non-parametric Mann-Whitney test was used to compare quantitative variables (Chan, 2003a). The Chi square test was employed to compare categorical data. When the anticipated frequency is less than five, an exact test was used instead (Chan, 2003b).

The threshold of 0.05 for a P-value was deemed statistically significant.

RESULTS:

A) Descriptive Data

Among the studied population there were 23 males and 107 females. The mean age was 42.65 years (SD = 11.9, minimum= 18.0 and maximum= 70.0). All patients had stage I papillary thyroid cancer. The mean size of the primary tumor in our study population was 2.0 cm (SD = 1.4, minimum= 0.1 and maximum= 8.0). 33.8% had normal thyroid tissue remnant. The most commonly encountered thyroid background pathology population was Hashimoto's thyroiditis (24.6% of patients), followed closely by MNG (23.1%). 18.5% had colloid nodular goiter. Further details of the histo-pathology are summarized in **Table 1**. The average time between thyroidectomy surgery and ablative dose was 5 months (SD = 2.4, minimum = 1 and maximum = 11). As regards the ablative dose received, 76.2% (n= 99) of our patients received 100 mCi while 23.8% (n= 31) received 80 mCi. Post-therapy scan was positive for thyroid residual and negative for loco-regional or distant metastases in all our patient population. Diagnostic post 6-months scan was positive in 29.2% (n= 38) of cases indicating incomplete ablation and was negative in 70.8% (n= 92) indicating complete ablation. As regards the laboratory parameters, baseline and post 6 months stimulated TG and stimulated anti-TG were evaluated for each patients and their results are summarized in **Table 2**.

Table 1: Histopathological background in our study population

		Count	%
Non-malignant thyroid tissue background	**Normal**	44	33.8%
	Hashimoto Thyroiditis	32	24.6%
	MNG	30	23.1%
	Colloid nodular goiter	24	18.5%
Focality	**Uni-focal**	58	44.6%
	Multi-focal	72	55.4%
Extra-thyroid extension	**Yes**	2	1.5%
	No	128	98.5%

Table 2: Descriptive analysis for quantitative laboratory parameters

		Mean	SD	Median	Min.	Max.
Baseline	sTG (ng/ml)	18.9	46.5	4.1	0.04	436.00
	s Anti-TG (ng/ml)	81.8	157.0	21.6	0.15	918
Post 6 months	sTG (ng/ml)	0.80	2.0	0.20	0.03	19.1
	s Anti-TG (ng/ml)	56.5	121.8	15.7	0.50	774.2

B) Correlative analysis

As regards the ablation outcome in relation to the background tissue, complete ablation after the first RAI dose was found in: 37 of the total of 44 patients (84.1%) with normal thyroid tissue background, in only 14 cases out of the total of 32 patients (43.8%) with Hashimoto's thyroiditis background, 24 of the total of 30 patients (80.0%) with MNG background, and 17 out of the total of 24 patients (70.8%) with colloid nodular goiter background. The difference between complete and incomplete ablation in relation to the thyroid tissue background was statistically significant with a p-value of <0.001. **Table 3** illustrates the comparison between complete and incomplete ablation after the first RAI dose in relation to the non-malignant thyroid tissue background.

Comparison of ablation outcome was performed between each group of patients individually versus normal thyroid tissue, and showed that only Hashimoto's thyroiditis had a statistically significant different ablation outcome, whereas the ablation outcome in the group of patients with MNG and colloid nodular goiter was not statistically different when compared to normal thyroid tissue. The comparison is shown in **Table 4**.

Table 3: Comparison between complete and incomplete ablation after the first RAI dose in relation to the non-malignant thyroid tissue background.

		Ablation Outcome				
		Complete		Incomplete		p-value
		Count	Percent	Count	Percent	
Non-malignant thyroid tissue background	Normal	37	84.1%	7	15.9%	<0.001
	Hashimoto Thyroiditis	14	43.8%	18	56.3%	
	MNG	24	80.0%	6	20.0%	
	Colloid nodular goiter	17	70.8%	7	29.2%	

Table 4: Comparison between each group of patients versus normal thyroid tissue as regards ablation outcome

	p-value
Normal thyroid tissue versus Hashimoto thyroiditis	<0.001
Normal thyroid tissue versus MNG	0.650
Normal thyroid tissue versus colloid nodular goiter	0.222

We categorized the patients into 3 groups according to the pathophysiology of the background thyroid tissue into 3 groups: Group A: Normal thyroid tissue, Group B: autoimmune pathology (including patients with Hashimoto's Thyroiditis), Group C: non-autoimmune pathology (including patients with MNG and CNG). There was a

statistically significant difference in the ablation outcome between patients with autoimmune pathology and patients with non-auto-immune pathology with a p-value of p<0.001. **Table 5** shows the comparison between complete ablation and incomplete ablation in relation to the presence of an auto-immune pathology. As regards the baseline tumor markers, there was a statistically significant lower mean value of baseline stimulated anti-TG in compete ablation (mean was 60.73) compared to incomplete ablation (mean was 132.81) with a p-value of p=0.018, while the difference in stimulated TG value in the two groups was not statistically significant. The comparison between complete and incomplete ablation in relation to the baseline tumor marker levels is summarized in **Table 6**. There was no statistically significant difference between complete and incomplete ablation according to other factors, including the ablative dose (p=0.380), post-operative neck U/S remnant tissue (p=0.775), baseline sTG (p=0.806), sex (p=0.384), focality (p=0.117) and extra-thyroid extension (p=1.000). Hashimoto's thyroiditis was a significant independent predictor factor for I-131 ablation outcome on univariate and multivariate regression analyses. (p-value= 0.002, OR= 0.217) with 95% C.I (0.083-0.563).

Table 5: Comparison between complete and incomplete ablation after the first RAI dose in relation to auto-immune background

		Ablation Outcome				
		Complete		**Incomplete**		**p-value**
		Count	**Percent**	**Count**	**Percent**	
Non-malignant thyroid tissue background	**Normal thyroid tissue (group A)**	37	84.1%	7	15.9%	<0.001
	Auto-immune origin (group B)	14	43.8%	18	56.3%	
	Non-autoimmune origin (group C)	41	75.9%	13	24.1%	

Table 6: Comparison between complete ablation and incomplete ablation according to baseline tumor marker levels

		Ablation outcome		p-value
		Complete	**Incomplete**	
Baseline sTG	Mean ±SD	20.78 ± 54.01	14.21±18.18	0.806
Baseline sAnti-TG	Mean ±SD	60.73 ±131.94	132.81 ±198.24	0.018

DISCUSSION:

Thyroid cancer that has undergone differentiation (DTC) is the most prevalent endocrine cancer, making about one percent of all cancer diagnoses annually. Roughly 90% of thyroid malignancies are well-differentiated thyroid tumors, of which PTC makes up 75–80% [(1).] PTC may manifest in the context of healthy thyroid tissue or in conjunction with benign thyroid conditions. Numerous research papers have been published in the literature on the incidence of PTC with other benign thyroid disorders. The prevalence of incidental papillary carcinoma (IPC) in benign surgically resected thyroid conditions was found to be twelve percent overall in a research conducted by Bradly had et colleagues [(7).] The research also indicated that Hashimoto's thyroiditis is connected with the greatest risk of IPC. According to a previous study by Farkas et al, 8% of patients needed a complete thyroidectomy for benign lesions that were detected by an IPC after a post-thyroidectomy [(8).] There have been conflicting reports about the prevalence of PTC and lymphocytic thyroiditis, ranging from 0.3 to 38 percent [(9, 10).] The wide range may be explained by several factors such as heterogeneous patient characteristics, different diagnostic criteria for CLT, and various sample size [(11).] In this study, which evaluated 130 patients with PTC, 33.8% of the patients had normal background thyroid tissue, while 24.6% had a background of lymphocytic thyroiditis, 23.1% had MNG and 18.5% had colloid nodular goiter. Our study showed that the thyroid tissue background was a statistically significant factor in the ablation outcome. After a single ablative dose of RAI-131, the success rate of ablation was much lower in patients with autoimmune thyroid diseases (Hashimoto's thyroiditis) than in those with normal thyroid

tissue or other non-autoimmune histology. Moreover, there was statistically insignificant difference in the ablation result between the subjects with normal thyroid cells and the subjects with non-autoimmune histo-pathologies. This comes in line with the laboratory parameters, where we found that the baseline stimulated anti-TG levels (which are known to be high in autoimmune thyroiditis [12]. were significantly lower in patients with successful ablation. Our findings broadly agree with those of a research by **Wagieh et al.** which had 124 patients [13]. A p-value of $p< 0.001$ was obtained when they discovered that, following a single ablative dose of RAI-131, the ablation rate was less successful in patients with a background of auto-immune histopathology (Hashimoto's thyroiditis or auto-immune thyroiditis), with an incomplete ablation in 65.1 percent of cases, compared to those with other histopathology (34.4 percent) as well as those with normal tissue from the thyroid (20 percent). In a study conducted on 691 patients with PTC, Kwon et al also found that coexisting Hashimoto's thyroiditis was inversely associated with initial radioactive-iodine remnant ablation success (50.7% of patient with Hashimoto's Thyroiditis vs 67.4% of patients without Hashimoto's thyroiditis; $p< .001$) [14]. **Albano** et al. [15] corroborated these findings by showing that Hashimoto's thyroiditis may impact RAIT effectiveness in low- to intermediate-risk DTC patients by decreasing the success rate of good response to RAIT. According to their findings, DTC patients with co-occurring Hashimoto's thyroiditis had a lower incidence of good response after a year (54 percent vs. 69 percent; $p<0.001$) than DTC patients without the condition. Additionally, they discovered that DTC patients with concurrent Hashimoto's thyroiditis had a lower 5-year good response rate (79 percent vs. 94 percent; $p<0.001$) than DTC patients without the condition. However, compared to PTC patients with no histopathologic evidence of CLT, Sayed et al. observed that patients with CLT had a much better result and a greater success rate of RAI-131 ablation [16]. Their findings demonstrated that after first RAI ablation, 90% of PTC patients with concomitant CLT had effective ablation, compared to 63.3% of patients without CLT. The existence of thyroid autoantibodies in CLT was cited as the explanation for these findings because they trigger an autoimmune reaction to antigens unique to the thyroid, that may lead to the death of thyroid cancer cells. These antibodies may be one of the ways that CLT helps DTC patients have a better prognosis

and reduce their risk of metastasis or recurrence [17, 18, 19]. According to other observations, PTC patients may show cytotoxic T-cell-mediated responses when they have thyroiditis [20]. Thus, CLT may enhance the therapeutic efficacy of RAI-131 by aiding in the death of cancer cells and halting the formation of new tumors via humoral and cytotoxic immune responses. The failure of individuals with auto-immune thyroiditis to react to elevated blood TSH levels and consequent incapacity to undergo effective iodine organification and storage might perhaps account for the results of our investigation. This may be explained by the widespread infiltration of mononuclear inflammatory infiltrates into the thyroid parenchyma. Thyroid follicles, that are in charge of absorbing iodine, shrink as a consequence. Because of this, thyroid follicles lining Hashimoto's thyroiditis are bordered by epithelial cells that are identified by the presence of a large amount of eosinophilic granular cytoplasm known as Hürthle cells. Hashimoto's thyroiditis is identified by the presence of these Hürthle cells conjugated with lymphocytes in fine needle aspiration biopsies [21]. Hashimoto's thyroiditis has two types: the classic form, which is characterised by an increase in interstitial connective tissues that may be profuse, and the fibrous variant, which is characterised by severe thyroid follicular atrophy and thick fibrosis. [22]. The existence of auto-antibodies against NIS is another explanation for ablation resistance in Hashimoto's thyroiditis patients [23]. The iodide transport process is inhibited by these antibodies. Nonetheless, more recent research revealed that anti-NIS antibodies are only slightly more common (less than 10%) in cases of Hashimoto's thyroiditis, raising questions about their practical significance [24, 25]. In summary, the various cellular resistance mechanisms displayed by the non-neoplastic thyroid tissue in the background of auto-immune thyroiditis may work in concert to decrease the uptake of radioactive iodine, resulting in a lower dose of radiation absorbed and, ultimately, a higher failure rate to the initial ablation dose. This research concluded that the ablation result by RAI was significantly influenced by the histology of the background non-neoplastic thyroid tissue residual in individuals with PTC. In particular, compared to patients with non-autoimmune histology and patients with normal thyroid tissue, patients with auto-immune thyroiditis had a considerably poorer ablation result rate after the first dosage of RAI. There was statistically insignificant difference in ablation outcome between the

latter two groups in our study. We recommend to perform a randomized study on a large number of patients with DTC to confirm and validate the above-mentioned data. Also, RAI-131 ablation therapy dose should be individualized according to different predictors of successful ablation outcome, i.e. patients with pathological evidence of thyroiditis in the background thyroid tissue should be given a higher dose of RAI to ensure complete ablation after the first dose. A potential limitation of the current study is its retrospective single-center study design with a limited number of subjects. Further prospective multi-center studies with a larger sample size may be considered to validate our findings.

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