Correlation of diffuse hepatic uptake with stimulated thyroglobulin levels and remnant thyroid uptake in post-radioiodine ablation scintigraphy among patients with differentiated thyroid cancer

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ABSTRACT

Introduction: Diffuse hepatic uptake in post-radioiodine treatment whole-body scans is commonly observed. This study explored the correlation between hepatic absorption intensity, stimulated serum thyroglobulin levels, and remnant thyroid uptake in post-treatment whole-body scans.

Methods: This cross-sectional study analyzed 120 post-treatment whole-body scans from 60 patients. Fixed regions of interest (ROIs) in the liver, thyroid, and thigh areas were considered, and absorption values were systematically calculated. Patient information including corrected hepatic uptake, corrected remnant thyroid uptake, and thyroglobulin levels-was collected and subjected to statistical analysis.

Results: Statistical analysis revealed that stimulated pre-treatment Tg level (p=0.882), hepatic uptake (p=0.114), and remnant thyroid uptake (p=0.836) in post-treatment whole-body scans, had no statistical difference between the responded and non-responded groups. There was a significant positive association between stimulated pre-treatment Tg level and remnant thyroid uptake only in the responded group (p=0.001, r=0.586). Stimulated pre-treatment Tg level had no significant association with hepatic uptake in total patients (p=0.927), responded (p=0.831), and non-responded group (p=0.906). Assessing the relation of administered iodine amount with thyroid remnant uptake, revealed that there was a significant and reverse association between administered iodine amount and remnant thyroid uptake (p=0.000, r=-0.499).

Conclusion: Hepatic uptake, stimulated thyroglobulin levels, and the remaining thyroid tissue did not correlate with treatment response rates. A positive relationship exists between hepatic uptake and remaining thyroid uptake. A positive relationship only exists between stimulated pre-treatment Tg level and remnant thyroid uptake in the responded group. Additionally, a significant negative correlation with iodine intake suggests that the thyroid may be saturated.

Keywords: Hepatic uptake; Radioiodine scintigraphy; Remnant thyroid tissue; Thyroid cancer; Thyroglobulin level

INTRODUCTION

The thyroid gland functions as an endocrine organ producing thyroid hormones, namely thyroxine (T4) and triiodothyronine (T3), through the incorporation of iodine into the amino acid tyrosine. These hormones serve as metabolic regulators within tissues [1]. Their impact on metabolism includes the promotion of specific protein synthesis, crucial for heat production and the maintenance of human body temperature. Additionally, thyroid hormones play a pivotal role in carbohydrate, protein, and lipid metabolism, facilitating energy supply to the body. During embryonic and postnatal phases, thyroid hormones are vital for the development of the nervous system [2]. Comparable to growth hormones, thyroid hormones contribute to bone growth. Overall, thyroid hormones are indispensable for the formation of teeth, hair, skin, and the proper functionality of the nervous, cardiac, and digestive systems [1].

Thyroid nodules manifest as discernible enlargements within the thyroid gland, exhibiting a distinct morphology from the typical appearance of the thyroid. A proportion of these nodules are concomitant with the potential peril of malignancy [3]. The pivotal challenge in managing thyroid nodules lies in distinguishing between benign and malignant entities [4]. Differential diagnosis involves a comprehensive approach encompassing patient history, physical examination, laboratory tests, neck ultrasound, and, in specific cases, needle sampling. Radionuclide scanning is reserved for instances where the patient exhibits a diminished TSH level [5].

Thyroid cancer stands as the predominant endocrine malignancy, constituting 1.5% of all cancers in the United States. The upswing in thyroid cancer prevalence is attributed to advancements in imaging techniques, leading to the identification of smaller nodules. This annual increase amounts to 5%, yet it has not precipitated significant alterations in disease mortality [6, 7]. Notably, thyroid cancer is highly treatable with a favorable prognosis [8]. Key risk factors for thyroid cancer development include radiation exposure, insufficient dietary iodine, exposure to nitrates, and air pollution [9].

The predominant manifestation of thyroid cancer, comprising over 95% of cases, arises from the epithelial cells of thyroid follicles. Differentiated thyroid cancer subtypes encompass papillary thyroid cancer, follicular thyroid cancer, Hurtle cell, and poorly differentiated thyroid cancer. Importantly, cells in this cancer type exhibit iodine absorption capability, rendering them amenable to treatment with radioactive iodine [7].

Papillary thyroid cancer, the most prevalent subtype, typically manifests in individuals aged 20-50. Follicular cancer, the second most common thyroid cancer, typically affects women aged 40-60 with iodine deficiency. Follicular cancer, along with Hurtle cell and poorly differentiated thyroid cancer, poses a heightened risk of distant metastases, particularly to bones and lungs via the bloodstream [5]. Although the prognosis is acceptable, it is lower than that of papillary thyroid cancer. Treatment for thyroid cancer involves surgery, radioactive iodine therapy, and TSH suppressor therapy. Before treatment, a crucial risk assessment is performed using cervical ultrasound, offering vital information on tumor size, location, lymph nodes, and invasion, guiding the surgical plan [10-12]. Numerous patients diagnosed with differentiated thyroid cancer (DTC) following total thyroidectomy and radioablation therapy exhibit diffuse hepatic uptake of radioiodine (Figure 1), a phenomenon whose clinical significance remains a subject of debate. Some researchers have indicated that this diffuse liver uptake is associated with uptake in the thyroid bed or the existence of metastatic thyroid cancer in other regions of the body, while others have found no such association [13]. The objective of this study was to assess the clinical relevance of diffuse hepatic uptake of radioiodine after 131I ablative therapy in individuals with DTC.

METHODS

Study design and population

This study is a cross-sectional investigation focusing on individuals who were admitted to our department. To qualify for inclusion, patient must meet specific criteria: they must undergone total thyroidectomy and have discontinued levothyroxine one month prior to iodine treatment. Additionally, patients must have undergone assessments of thyroid stimulating hormone (TSH), along with evaluation of thyroglobulin and anti-thyroglobulin levels, conducted 6 to 12 months after treatment. They should also have post treatment be considered for inclusion, patients must meet specific criteria, including having undergone a total thyroidectomy, discontinuing levothyroxine tablets one month prior to iodine treatment, 6 to 12 months post-treatment assessments of TSH along with evaluation of thyroglobulin, and anti-thyroglobulin levels conducted 6 to 12 months after treatment. They should also have post-treatment whole body scan, as well as follow up scans 6 to 12 months later in patients who did not have distant metastasis. Patients who lack the required blood work, diagnostic and therapeutic scans, or surgical pathology reports available in their medical files were excluded from the study.

Data collection and analysis

Patients' information and lab data were extracted. Therapeutic and diagnostic scans were obtained from the nuclear medicine department filing system. Regions of interest (ROI) were delineated around the liver and thyroid gland and the corrected count rate was calculated (average count rate - background count rate/background count rate). Data was entered into the SPSS 24 program for analysis, employing descriptive statistics (frequency, percentage, mean, and standard deviation) and inferential statistics (t-test, Pearson correlation coefficient). The significance difference was set at p-value < 0.05.

RESULTS

In this investigation, a cohort of 60 individuals diagnosed with thyroid cancer who had undergone iodine treatment was analyzed. The average age of the participants was 44.17±13.4 years. The study comprised 53 female patients (88.3%) and 7 male patients (11.7%). Within this sample, 58 individuals (96.7%) were diagnosed with papillary thyroid cancer, while 2 individuals (3.3%) had follicular thyroid cancer. The administered iodine doses varied depending on the type, severity, and extent of the disease: less than 100 mCi was given to one patient, 100 mCi to 18 patients, 125 mCi to 16 patients, 150 mCi to 22 patients, 175 mCi to 2 patients, and 200 mCi to one patient. Detailed information on patient subgroups, specifically the respondent and non-responded groups, is presented in Table 1.

According to the latest guidelines set by the American Thyroid Association (ATA), "disease-free status" (responded group) is characterized by the absence of any clinical signs of tumor, no detection of tumor through radioactive iodine (RAI) imaging or ultrasound, and unstimulated thyroglobulin (Tg) below 0.2mg/ml or stimulated Tg below 1mg/ml in the absence of antibodies [14].

Among 60 patients, the distribution of stimulated pre-treatment serum Tg levels was as follows: 35% (n=21) had Tg levels ranging from 0-1, 45% (n=27) had levels between 1-10, 15% (n=9) fell within the 10-30 range, and 5% (n=3) exceeded 30. The distribution of stimulated pre-treatment Tg levels across subgroups is presented in Table 2 [15].

During the follow-up period, 30 out of 60 patients (50%) responded to the treatment (disease-free status), while the remaining 30 did not respond. Among those who did not respond, 12 had a positive scan, two had both a positive scan and ATA levels over 100 IU/mL, and one had a positive scan along with stimulated Tg levels exceeding 1 ng/mL. Of the 15 patients who showed no improvement and had negative scans, two had ATA levels over 100 IU/mL, and 13 had stimulated Tg levels above 1 ng/mL (two of whom had increased Tg levels during follow-up despite having levels below 1 ng/mL before treatment). According to the data presented in Table 3, there were no significant differences in pre-treatment Tg level, hepatic uptake, and remnant thyroid uptake in post-treatment WBS (ptWBS) between the groups that responded and did not respond.

The association of stimulated pre-treatment Tg level and other variables in total patients and subgroups are shown in Table 4. There was a significant positive association between stimulated pre-treatment Tg level and remnant thyroid uptake only in the responded group (p=0.001, r=0.586). Stimulated pre-treatment Tg level had no significant association with hepatic uptake in total patients (p=0.927), responded (p=0.831), and non-responded group (p=0.906).

The association of hepatic uptake and remnant thyroid uptake in total patients and subgroups is shown in Table 5. There was a significant positive association between hepatic uptake and remnant thyroid uptake in the total patients (p=0.008, r=0.238), responded group (p=0.006, r=0.492), and non-responded group (p=0.005, r=0.496).

Assessing the relation of administered iodine amount with thyroid remnant uptake in total patients, revealed that there was a significant and reverse association between administered iodine amount and remnant thyroid uptake (p=0.000, r=-0.499). There was no significant relationship between administered iodine amount and hepatic uptake (Table 6).

DISCUSSION

In this study, there was no statistically significant difference in stimulated pre-treatment thyroglobulin (TG) levels, hepatic uptake, or remnant thyroid uptake in post-treatment whole-body scan (ptWBS) between the responded or non-responded groups. However, a significant positive association was found between hepatic uptake and remnant thyroid uptake across all patients, as well as within both the responded and non-responded groups. Additionally, a significant positive association was observed between tg levels and thyroid remnant uptake specifically in the responded group (P=0.001, r=0.568). When examining the relationship between the amount of iodine administered and thyroid remnant uptake across all patients, a significant inverse association was identified; higher amount of administered does were associated with lower remnant thyroid uptake (p=0.000, r=-0.499). However, there was no significant relationship between the administered iodine dose and hepatic uptake.

In the study of Tatar et al., 141 scans of patients were examined after treatment, and hepatic uptake was qualitatively graded between 0-4, each patient was placed in one category, and the information of patients in each category was based on thyroglobulin level. The presence or absence of residual thyroid tissue and the mortality rate were investigated. It was concluded that the level of hepatic uptake is not related to any of these results [13].

In a study by Jun et al. [16], only patients with metastases were examined, and their hepatic uptake and thyroglobulin levels were examined during the course of the disease, and it was concluded that the severity of hepatic uptake is associated with a decrease in thyroglobulin levels in the future. It can be a factor in predicting responses to treatment.

In the study of Kim et al. [17], scans of 838 postnatal patients were examined and the degree of liver and thyroid uptake were qualitatively classified and the response to treatment was examined accordingly. It was finally determined that Patients with low hepatic uptake in the presence of high thyroid uptake do not respond well to treatment, and it is probably due to insufficient post radiation treatment response (destruction) of thyroid tissue. In this study, the relationship between the level of thyroglobulin and the severity of hepatic uptake was not investigated.

In the previous studies, [18-20] uptake of the liver and remnant of the thyroid was evaluated qualitatively. In this study, to avoid visual and individual errors caused by qualitative classification, the hepatic and remaining thyroid tissue uptake was evaluated based on ROI, and patients were divided according to thyroglobulin level.

CONCLUSION

Hepatic uptake, stimulated thyroglobulin levels, and the remaining thyroid tissue did not correlate with treatment response rates. A positive relationship exists between hepatic uptake and remaining thyroid uptake. A positive relationship only exists between stimulated pre-treatment Tg level and remnant thyroid uptake in the responded group. Additionally, a significant negative correlation with iodine intake may suggest thyroid saturation.

ACKNOWLEDGMENT

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Table 1. Characteristics of patients

		Responded group N=30 n(%), Mean±SD	Non-responded group N=30 n(%), Mean±SD
Age (year)		44.3±11.8	44±14.9
Gender	Female	27 (90%)	26 (86.7%)
	Male	3 (10%)	4 (13.3%)
Pathology	Papillary	29 (96.7%)	29 (96.7%)
	Follicular	1 (3.3%)	1 (3.3%)
Scan	Positive	0	15 (50%)
	Negative	30 (100%)	15 (50%)
Iodine dosage (mCi)	Below 100	0	1 (3.3%)
	100	9 (30%)	9 (30%)
	125	7 (23.4%)	9 (30%)
	150	14 (46.6%)	8 (26.7%)
	175	0	2 (6.7%)
	200	0	1(3.3%)

Table 2. Pre-treatment thyroglobulin level and follow up outcome

Stimulated Pre-treatment Tg level (ng/mL)	**Follow up outcome**					
		Non-responded group				
	Responded group (n)	Only Tg>1 ng/mL (n)	Only positive scan (n)	Positive scan and Tg>1 ng/mL (n)	Only ATA>100 IU/mL (n)	ATA>100 IU/mL and positive scan (n)
0-1 (n=21)	10	2	6	0	1	2
1-10 (n=27)	15	7	4	0	1	0
10-30 (n=9)	4	3	1	1	0	0
>30 (n=3)	1	1	1	0	0	0

Table 3. Comparison of variables between responded and non-responded groups to treatment

	Responded group (mean±SD)	Non-responded group (mean±SD	P value †
Stimulated Pre-treatment Tg level (ng/mL)	8.8±5.6	10.6±7.1	0.882
Hepatic uptake in ptWBS	9.1±6.9	4.17±4.01	0.114
Remnant thyroid uptake in ptWBS	48.18±29.6	131.95±48.96	0.836

†Independent t-Test

Table 4. Association of Tg level and other variables

Stimulated Pre-treatment Tg level		Hepatic uptake	Remnant thyroid uptake
Total patients	p	0.927	0.621
	r†	0.012	0.605
Responded group	p	0.831	0.001*
	r	0.041	0.568
Non-responded group	p	0.906	0.676
	r	0.022	0.079

*Significant result
†Pearson correlation coefficient

Table 5. Association of Tg level and thyroid uptake

Hepatic uptake		Remnant thyroid uptake in ptWBS
Total patients	p	0.008*
	r†	0.238
Responded group	p	0.006*
	r	0.492
Non-responded group	p	0.005*
	r	0.496

*Significant result
† Pearson correlation coefficient

Table 6. Association of iodine dose and other variables

Iodine dose		Remnant thyroid uptake	Hepatic uptake
Total patients	p	0.000*	0.071
	r†	-0.499	-0.234

*Significant result
† Pearson correlation coefficient

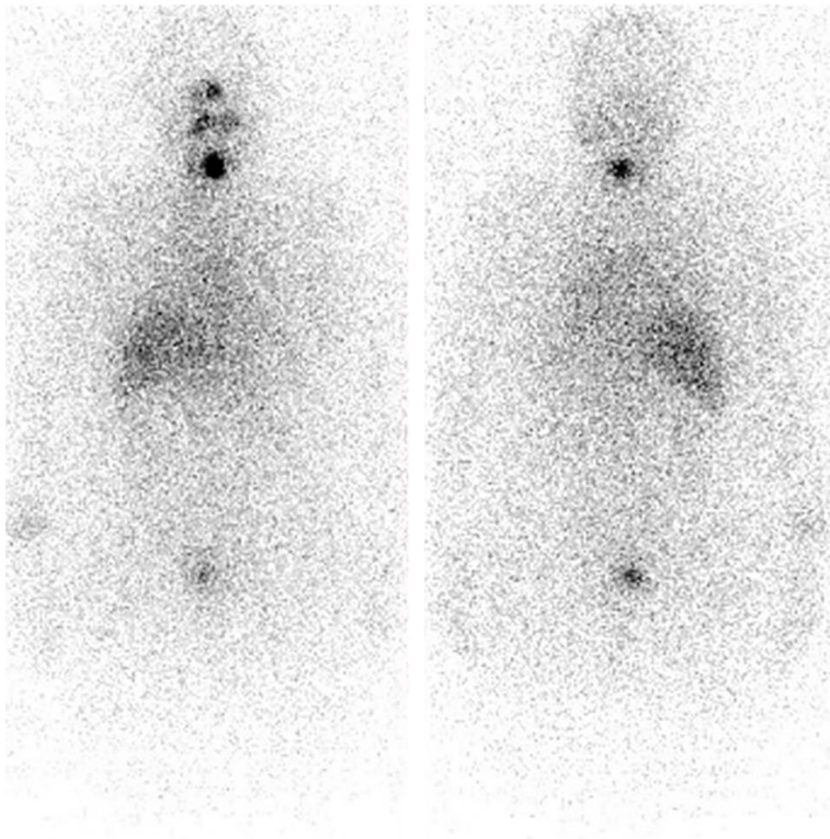

Figure 1. Anterior and posterior views of the radioiodine whole-body scan revealed intense remnant thyroid uptake in the neck as well as diffuse hepatic uptake likely due to post radiation thyroid tissue destruction and accumulation of released iodinated thyroid hormone in the liver