Original Paper, Endocrine.

Re-exploration of Radio-iodine Diffuse Hepatic Uptake as Early Prognostic Indicator in Differentiated Thyroid Carcinoma.

Hussein, E[1]. Abd El-Aleem, M[2] and El-Refaei SH[1].

[1]Nuclear medicine and radiation oncology department, faculty of medicine, Cairo University.

[2]Nuclear medicine, Beni-Sweif University

ABSTRCAT:

Background: The aim of this study was to explore the potential early prognostic value of radio-iodine diffuse hepatic uptake (DHU) in post-ablative whole body iodine scans (PAWBISs) of patients with low/intermediate risk differentiated thyroid cancer (DTC) and no evidence of disease. **Patients and Methods:** A total of newly diagnosed 100 patients with pathologically proven DCT presented in the department of nuclear medicine and radiation oncology, Cairo University were prospectively included; age (18-75-year-old); They were followed for a period of 30.9 ± 12.4months. Grades of hepatic and thyroid bed uptake PAWBISs were classified from 0 to 3 by visual assessment. Endpoints were no evidence of disease (NED), the persistence of disease or disease recurrence till the end of the follow-up period. Comparison of numerical variables between the study groups was done using Chi-square (c2) test. Exact test was used instead when the expected frequency is less than 5. Comparison was done between the different factors by Log-rank method using Cox-Mantel equation. Cox multivariate regression was used to determine the preferential effect of important variables. *p* values less than 0.05 was considered statistically significant. **Results:** DHU was observed in 87 PAWBISs; grade 1 'mild' uptake was observed in 28, grade 2 'moderate' in 46, grade 3 'marked' in 13 PAWBISs. Analysis of the different grades of DHU in the low and high dose groups of patients showed significant association with the outcome (p 0.001)**.**

Univariante analysis showed that the grade of DHU (p 0.005) as well as the patient gender, age, primary tumor size and cervical LN status are statistically significant predictors of the outcome. Multivariate analysis also showed that the grade of DHU, patient gender and tumor multiplicity and are the only independent prognostic factors with p values 0.048, 0.042, 0.009 respectively.

Conclusion: more intense visualization of DHU on PAWBIS is considered as an independent prognostic factor associated with a better outcome in low/intermediate risk DTC patients than its faint visualization which may be related to ineffective thyroid cells destruction in the latter.

Key words: *Differentiated thyroid cancer, diffuse hepatic uptake and prognosis.*

Corresponding Author: Hussein, E. **E-mail:**elshaymaa_hussein@yahoo.com.

INTRODUCTION:

Differentiated thyroid carcinoma (DTC) usually carries a good prognosis in most patients; however, some of the patients may suffer from persistence or recurrence of the disease [(1)]**.** An early and accurate method for prognostication is still lacking to determine these patients who will need intensification of the therapy as well as the follow-up plan aiming to improve their quality of life [(2)]**.** Hepatic visualization is described as a common finding in whole body radio-active iodine scan (WBIS) since 1987[(3)], however its prevalence and prognostic significance are not well understood [(4, 5)].

Aim of the work: to re-explore the potential early prognostic value of radio-iodine diffuse hepatic uptake (DHU) in post-ablative whole body iodine scans (PAWBISs) of patients with low/intermediate risk differentiated thyroid cancer (DTC) and no evidence of disease.

PATIENTS AND METHODS:

1. Study design*:* A prospective Cohort study included one- hundreds (100) consecutive adults patients presented in the nuclear medicine unit, faculty of medicine, Cairo university with newly diagnosed low/intermediate risk differentiated thyroid carcinoma (DTC) status post total/near total thyroidectomy with or without neck dissection and no clinical or radiological evidence of local residual or remote metastatic disease.

The study was approved by the department review board, and written informed consent was obtained from all patients.

2. Initial post- operative risk stratification: All patients underwent; initial post-operative evaluation including personal history taking including the most important known risk factors as sex, age and previous exposure to neck irradiation, meticulous clinical examination as examination of the neck for palpable residual disease, regional groups of lymph nodes and liver examination and Laboratory and radiological investigations in the form of:

1) Baseline serum thyroglobulin (TG). Patients with elevated TG levels were investigated for remote disease to be excluded.

2) Serum TSH at least 4 weeks after surgery and/or withdrawal of Eltroxin.

3) Liver function tests: SGOT, SGPT, ALK.P, serum albumin; to exclude serious liver impairment disease.

4) Complete blood picture, Kidney function tests Pregnancy test (β-hCG); to ensure feasibility for RIA.

5) Neck ultrasound for assessment of thyroid residue or cervical lymph nodes.

6) X-ray chest or CT chest without contrast.

All patients were stratified according to the risk stratification criteria of the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [(6)].

3. Radioactive iodine Ablation (RIA): Patients were treated according to the department's protocol in respect of their risk groups**.** The dose of radioactive iodine was decided empirically in the range of 1.1- 5.55 GBq (30 -150 mCi).The patients received their respective doses as capsules administered orally at least 4 weeks following surgery or after withdrawal of thyroid hormone medications and achieving a serum level of TSH > 30 IU/ml. 70 patients received high doses of 2.9- 5.5 GBq (80-150mCi) and 30 patients received low doses of 1.1 GBq (30mCi).

4. Post-ablative whole body iodine scan (PAWBIS) acquisition:

1) Patients performed their PAWBISs 7 - 10 days post RIA. The scans were obtained with large F-O-V dual-head gamma camera (Philips-Axis, Eindhoven, the Netherlands).

2) Anterior and posterior whole-body images were acquired with a high-energy parallel-hole collimator. 20% window was centered on the principle photo-peak of I-131 (364 keV).

5. Analysis of PAWBIS images: The intensity of DHU visualization in $PAWBIS_S$ was graded visually in consensus by three nuclear physicians into the following **4 grades** relative to the background activity; **Grade 0:** No uptake, **Grade 1:** Faint uptake, **Grade 2:** Moderate uptake and Grade **3:** Marked uptake. The intensity of thyroid bed remnant uptake (TBU) was also similarly classified ***(Figure 1)*.**

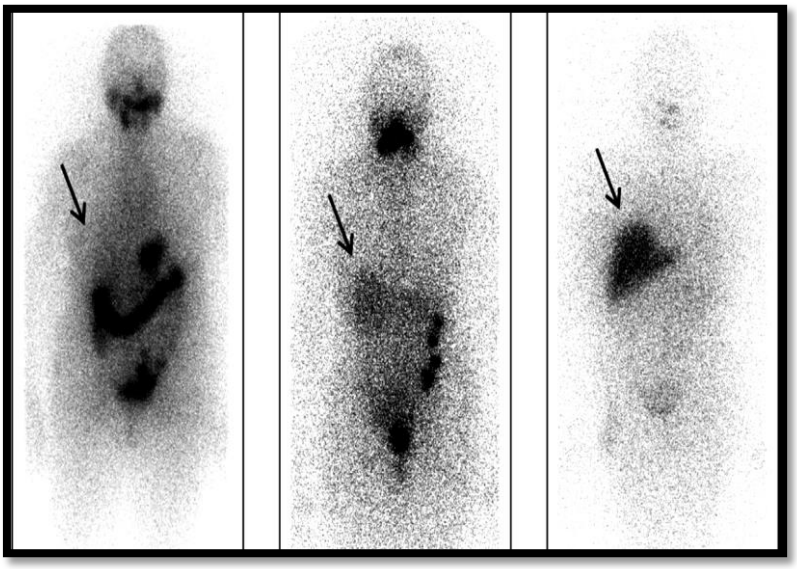

Fig. 1: Visual grading of DHU relative to the background activity; left image (Grade 1): Faint uptake, middle image (Grade 2): Moderate uptake and right image (Grade 3): Marked uptake.

1. Follow-up

Patients were followed for a minimum period of 24 months (mean 30.9 ± SD12.4) or until radiologic and/or histopathologic evidence of disease persistence/ recurrence. Disease status updated during clinical follow-up visits by;

meticulous clinical examination, diagnostic whole body iodine scan (DWBIS), stimulated serum TG, Anti-TG-AB, Neck ultrasound and CT /chest/abdomen or ^{18}F-FDG-PET/CT when indicated.

2. Patient outcome criteria: by the end of the follow-up period ; patients are considered to be either with ;

(1) **No evidence of disease (NED)** which was defined by undetected serum TG, no evidence of local or remote disease on DWBS and no evidence of local disease in neck ultrasound.

(2) **Persistent or recurrent disease which was** defined by the presence of any of the following events during follow-up: increased stimulated serum thyroglobulin (Tg) level, Iodine-131 avid lesions in the DWBIS, suspicious LNs in neck US, evidence of metastatic deposits by CT or MRI and 18F-FDG avid lesions when indicated+/- histo-pathological evidence of disease.

Statistical Analysis: Data were statistically described in terms of frequencies (number of cases). Comparison of numerical variables between the study groups was done using Chi-square ($\chi 2$) test. Exact test was used instead when the expected frequency is less than 5. Comparison was done between the different factors by Log rank method using Cox-Mantel equation. Cox multivariate regression was used to determine the preferential effect of important variables. *p* values less than 0.05 was considered statistically significant. Survival analysis was done for the different outcome measures using Kaplan Maier statistics calculating the mean and median survival time for each group with their 95%CI and the corresponding survival graphs. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release22 for Microsoft Windows.

RESULTS:

1. Patients' characteristics: the demographic data of the patients are listed in ***Table (1)*****.**

2. Post ablative whole body iodine scan (PAWBIS) analysis:

DHU (grade 1-3) was observed in 87 PAWBISs, while the rest 13 scans show no visualization of the liver. Among these 87 PAWBISs, grade 1 'mild' uptake was observed in 28, grade 2 'moderate' in 46, grade 3 'marked' in 13.

The different levels of DHU were compared in both groups of patients according to the administered dose (low (30mci) and high (80-150mci) **(p value 0.004)** ***(Table 2)***.

Table 1: Demographic details of the 100 studied patients in relation to their outcome.

		Outcome		Total	*p* value
		NED	Persistent /Recurrent disease		
Sex	Female	63	3	66	**0.004***
	Male	25	9	34	
Age	< 45 year	69	2	71	**<0.005***
	≥45	19	10	29	
Pathology	Papillary	64	8	72	**0.253**
	Follicular	24	4	28	
Tumor Size	<1cm	70	3	73	**0.005***
	>1cm	18	9	27	
Tumor Multiplicity	Uni-focal	77	5	82	
	Multifocal	11	7	18	**0.02***
TNM Stage**	I	70	2	72	
	II	12	8	20	**0.03***
	III	6	2	8	
LN status	Negative	82	6	88	**0.05***
	Positive	6	6	12	
Risk group	Low	58	4	62	**0.06**
	Intermediate	30	8	38	
Total		**88**	**12**	**100**	

* Significant p value <0.05.

**TNM staging according to the updated American Joint Committee on Cancer for differentiated Thyroid Cancer [7].

Table 2: frequency of different DHU grades in both groups of patients.

Liver grade	Group		Total	*p* value
	Low dose	High dose		
No Uptake	7	6	13	
Mild	12	16	28	
Moderate	11	35	46	**0.004***
Marked	0	13	13	
Total	30	70	100	

*Significant p value <0.05.

Mild and moderate' grades of DHU were noted in 17 and 34 PAWBISs respectively in the high dose group of patients compared to 12 and 11 PAWBISs respectively in the low dose group of patients. Marked' grade of DHU was not observed in the entire low dose group of patients PAWBIS's compared to 13 cases noted in the high dose group of patients. Also, the number of 'No' hepatic uptake was higher in the low dose group with 7 cases compared to 6 in the high dose group ***(Table 2)*.**

Analysis of the different grades of DHU in the low and high dose groups of patients showed significant association with the outcome **(p 0.001).** Among the 88 patients with NED at the end of the study, 58 PAWBISs showed higher grades of DHU (grades 2 and 3), while low grades of uptake (grades 0 and 1) were noted only in 30 PAWBISs ***(Table3)***. Moreover, in all cases with persistent and recurrent disease; the liver grades were low (grade 0 and 1) ***(Table 3)*.**

In contrast, there was no association between the degree of the thyroid bed remnant uptake (TBU) with neither the administered dose nor the outcome **(p value: 0.471 and 0.404 respectively).**

By comparing the degree of DHU to the different clinical variables; it was not affected neither by age of patient **(p 0.564)**, gender **(p 0.107)**, tumor pathology **(p 0.808),** nor the base line thyroglobulin **(p 0.139).**

An analysis of variance revealed significant difference between the levels of uptake in the thyroid bed and visualization of the liver **(p 0.005)**. ***(Tables 4 and 5)*** combine cross-sectional degrees of both thyroid and liver uptake in the low and high dose groups. As the thyroid uptake increases, the liver visualization is more evident with **r = 0.552 & 0. 329** in the low and high dose groups respectively.

Table 3: frequency of different DHU grades in relation to the patient outcome**.**

Liver grade	Outcome		Total	*p* value
	NED	Persistent/ recurrent disease		
No	8	4	12	**0.001***
Mild	22	8	30	
Moderate	46	0	46	
Marked	12	0	12	
Total	**88**	**12**	**100**	

*Significant p value <0.05.

Table 4: cross-sectional tabulation of different DHU and thyroid uptake grades in the low dose group.

		Liver uptake grade			Total	p value	r factor
		No	Mild	Moderate			
Thyroid Uptake Grade	Mild	5	5	0	10	**0.005***	**0.552****
	Moderate	2	6	8	16		
	Marked	0	1	3	4		
Total		**7**	**12**	**11**	**30**		

*Significant p value <0.05.

**moderate positive correlation.

Table 5: Cross-sectional tabulation of different DHU and thyroid uptake grades in the high dose group.

			Liver uptake grade			Total	p value	r factor
		No	Mild	Moderate	Marked			
Thyroid uptake grade	**No**	0	0	1	1	2	**0.002 ***	**0.32 ****
	Mild	2	6	5	1	14		
	Moderate	4	8	15	10	37		
	Marked	0	5	11	1	17		
Total		**6**	**19**	**32**	**13**	**70**		

***** Significant p value <0.05.

** Moderate positive correlation.

3. Univariante analysis: The univariante analysis showed that the grade of DHU can predict outcome in the low and high dose groups of patients **(p value: 0.04 and 0.005** in the low and high dose groups respectively) as shown in ***Table (6)*** with relatively worse outcome in the lower grades (grade 0 and 1), and better outcome with the high grades (2 and 3).

On the other side, the grades of the thyroid uptake were not statistically significant regarding the outcome **(p value: 0.685)**. The conventional clinical and pathological factors such as patient gender, age, primary tumor size and cervical LN status were also statistically significant predictors of the outcome in the current study ***(Table 6)*.**

4. **Multivariate analysis:** In the high dose group; it showed that the patient gender, tumor multiplicity and grade of DHU, are the only independent prognostic factors with **p values 0.048, 0.042, 0.009 respectively *(Table 7)*.** Better outcome was noted in females, unifocal tumors and higher grades of DHU. In the low dose group; no one of the variables defined as significant predictor for the disease free survival and such finding may be attributed to the low sample of the low dose group compared to the high dose individuals.

Table 6: Univariante analysis of clinical, pathological factors, diffuse hepatic uptake grades and thyroid bed uptake grades.

Group		**Low dose**		**High dose**	
Variable		Mean	p value	Mean	p value
Sex	Male	37.540	**0.002***	39.072	**0.005***
	Female	44.762		54.679	
Age	<45	55.705	**0.001***	55.280	**0.05** *
	45 or more	30.867		29.684	
Pathology	Papillary	50.491	**0.668**	51.891	**0.361**
	Follicular	48.330		49.750	
Multiplicity	Uni-focal	50.145	**0.597**	54.964	**0.005** *
	Multifocal	42.545		24.786	
Tumor size	>1cm	24.764	**<0.005***	30.436	**0.001** *
	<1cm	54.625		54.600	
LN metastasis	Positive	31.000	**0.333**	28.153	**0.005**
	Negative	49.875		54.522	
TBU	**Global**	**-**	**0.312**	-	**0.685**
DHU	**Global**	**-**	**0.043**	-	**0.005 ***

*Significant p value <0.05.

Table 7: Multivariate analysis of clinical, pathological factors diffuse hepatic uptake and thyroid bed uptake.

Variable	Low dose group		High dose group	
	B factor	p value	B factor	p value
Sex	9.642	0.334	1.612	**0.048 ***
Age	2.974	0.400	0.938	**0.288**
Pathology	19.238	0.335	-0.726	**0.250**
Multiplicity	10.169	0.325	1.597	**0.042 ***
Size	10.700	0.287	-1.080	**0.358**
LN. status	-1.820	0.251	1.250	**0.175**
TBU	-0.260	0.835	0.116	**0.830**
DHU	-9.161	0.350	-1.333	**0.009***

*Significant p value <0.05.

5. **Event free-survival Analysis:**

The Event-free survival curves in the low and high dose groups of patients in relation to different grades of diffuse hepatic uptake are illustrated in ***Figures (2 and 3)***.

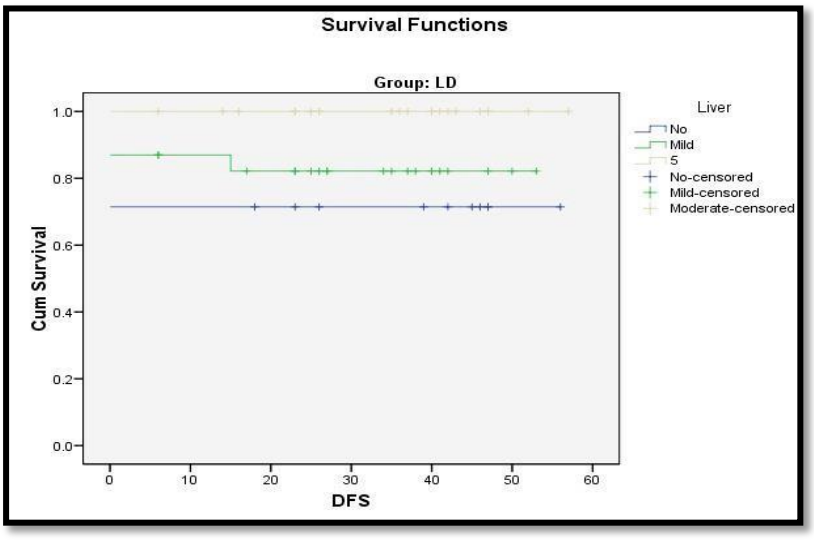

Fig. 2: Event-free survival curves in the low dose group of patients in relation to different grades of diffuse hepatic uptake.

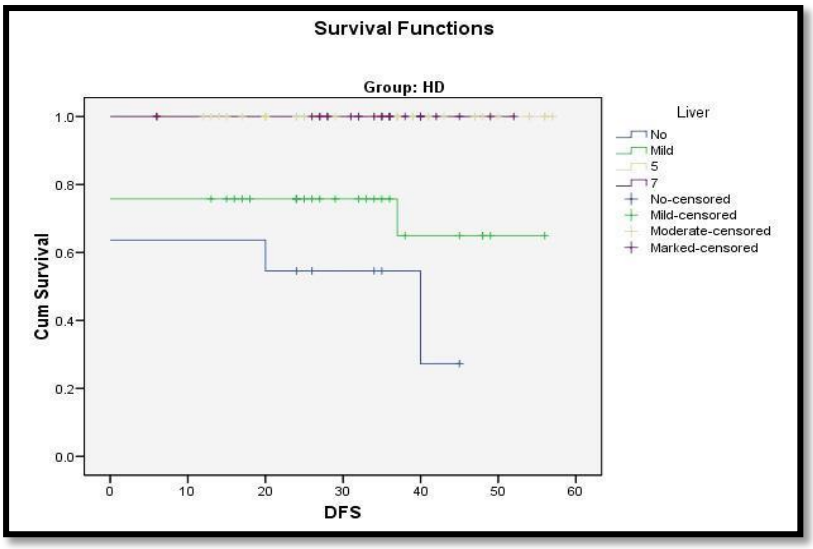

Figure 3: Event-free survival curves in the high dose group of patients in relation to different grades of diffuse hepatic uptake.

DISCUSSION:

DHU is a not an uncommon finding in WBISs [6]. However, its prevalence and significance either on diagnostic (DWBIS) or post ablative/ therapy WBIS (PA/PT-WBIS) is still controversial [7, 8]**.** The cause of this benign radioactive iodine uptake is not fully understood as iodine does not normally concentrate in the liver, and they likely relate this pattern of radio-iodine uptake to the metabolism of ^{131}I-labeled thyroglobulin liberated from functioning/destructed thyroid tissues [9].

In our cohort group; 87 (87%) patients showed different grades of DHU in their 1st PAWBIS. This relative high frequency is likely attributed to the delay of the imaging time (7-10 days) post-RAI intake. DHU was reported to be in the range of 35% to 96%; this wide percentile range was explained twice; firstly due to variation in the time of WBI scanning with the highest frequencies are seen around 6 to 8 days post RAI intake**,** secondly due to the variable doses of the included studies in the literature whether it is DWBIS (2-5mCi) or post-ablative/therapeutic RAI scans (PA/PT-WBIS) (>30mci) [10] as many reports relate DHU to a higher RAI dose and accordingly they concluded that the more I-131 administered; the more in vivo labeling will occur [5,10]. In our study we also investigated the effect of the radioactive ablative dose of iodine on the frequency and grade of DHU visualization. We found a statistically significant difference in between the low and high dose groups of patients ($p < 0.005$).

We observed that higher hepatic grades are noted in those patients receiving a higher ablative dose of RAI. Similarly, many other authors demonstrated that DHU was more commonly seen on (PA/PT-WBIS) rather than DWBISs. DHU ranged from 8.5% - 13% in the diagnostic WBISs and it ranged from 39% - 71% of the therapeutic scans in their studies [4, 11].

Other authors as ***Tatar et al,*** observed no DHU in all DWBISs in his study, while it was observed in 95.8% after receiving conventional RAI ablative doses [5].

There are contradictory results on the clinical significance of DHU in the published literature, especially regarding prognosis. In the present study, we found that the grade of DHU could be a predictor of patient's outcome and recurrence free survival. We observed that the higher the grade of uptake the better the outcome.

This is in line with the results of ***Kim et al,*** who reported that faint hepatic visualization along with intense thyroid bed remnant uptake (TBU) predict relatively worse prognosis, they concluded that this may be referred to insufficient thyroid tissue destruction [11].

Similarly, ***Jun et al,*** found that the intensity of DHU on PT-WBIS of patients with evident iodine avid disease is correlated with higher percentage of serum TG reduction and subsequent better prognosis [12].

CONCLUSIONS:

More intense visualization of DHU on PAWBIS is considered as an independent prognostic factor associated with a better outcome in low/intermediate risk DTC patients than its faint visualization which may be related to ineffective thyroid cells destruction in the latter, however, further studies with larger population and longer follow-up periods is needed.

REFERENCES:

1. ***Pitoia F, Bueno F, Urciuoli C, et al,.*** Outcomes of patients with differentiated thyroid cancer risk-stratified according to the American Thyroid Association and Latin American Thyroid Society risk of recurrence classification systems. Thyroid: 23: 1401–1407; 2013.

2. ***Lang BH, Chow SM, Lo CY, et al,.*** Staging systems for papillary thyroid carcinoma: a study of 2 tertiary referral centers. Ann. Surg.; 246:114–121; 2007.

3. ***Ziessman HA, Bahar H and Fahey FH et al,.*** Hepatic visualization on iodine-131 whole-body thyroid cancer scans. J. Nucl. Med. 28: 1408-1411; 1987.

4. ***Rosenbaum RC, Johnston GS and Valente WA,.*** Frequency of hepatic visualization during I-131 imaging for metastatic thyroid carcinoma. Clin. Nucl. Med. 13: 657-660; 1988.

5. ***Tatar FA, Morita E, Ituarte PH, at al,.*** Association between residual thyroid carcinoma and diffuse hepatic uptake of 131I following radioiodine ablation in postoperative total thyroidectomy patients. World J. Surg.; 25: 718-722; 2001.

6. ***Haugen BR, Alexander EK, Bible KC, et al,.*** 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. Jan; 26(1):1-133; 2016.

7. ***Tuttle RM, Haugen B, and Perrier ND.*** Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition): What Changed and Why?. Thyroid 27(6):751-756; 2017.

8. ***Ferris HA, Williams G, Parker JA, et al,.*** Therapeutic implications of diffuse hepatic uptake following I-131 therapy for differentiated thyroid cancer. Endocr. Pract. 19: +263–7; 2013.

9. ***Chung JK, Lee YJ, Jeong JM, et al,.*** Clinical significance of hepatic visualization on iodine-131 whole-body scan in patients with thyroid carcinoma. J. Nucl. Med. 38: 1191-1195; 1997.

10. ***Omur O, Akgun A, Ozcan Z, et al,.*** Clinical implications of diffuse hepatic uptake observed in post-ablative and post-therapeutic I- 131 scans. Clin. Nucl. Med. 34: 11-14; 2009.

11. ***Kim K, Kim SJ, Kim IJ, et al,.*** Clinical significance of diffuse hepatic visualization and thyroid bed uptake on post-ablative iodine 131 whole body scan in differentiated thyroid cancer. Oncology. 35:82–6; 2012.

12. ***Jun S, Lee J.J, Park S.H, et al,.*** Prediction of treatment response to 131I therapy by diffuse hepatic uptake intensity on post-therapy whole-body scan in patients with distant metastases of differentiated thyroid cancer. Annals of Nuclear Medicine: 29(7):603-12; 2015.