



Does hepatic visualisation show residual/metastatic thyroid tissue in differentiated thyroid cancer?

Physiological hepatic visualisation in differentiated thyroid cancer

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Abstract

Aim: Diffuse homogen hepatic uptake in whole-body scan (WBS) after radioiodine remnant ablation (RRA) suggests that there is occult or visible remnant thyroid tissue and/or tumor tissue. It is thought that the reason is hepatic metabolization of radioiodine (¹³¹I) marked thyroglobulin fragments which are secreted by remnant/tumor tissue. The aims of this study were to investigate whether the hepatic visualisation after radioiodine remnant ablation showed the presence of metastatic or residual disease in patients with differentiated thyroid cancer and also to investigate whether early or late WBS after RRA (RxWBS) had an effect on the physiological hepatic uptake. **Material and Method:** 201 DTC patients were evaluated (F/M: 152/49; mean age: 49.61±13 years (range: 18–85 years)) who referred for RRA. The therapeutic ¹³¹I dose ranged from 100mCi to 200mCi. RxWBS was performed earlier (in 1-4th-day after RRA) in 106 patients (Group 1) and was performed later (in 5-9th-day after RRA) in 95 patients (Group 2). **Results:** Diffuse hepatic uptake were seen only in three patients (2.8%) and was not seen in 103 patients (97.2%) in Group 1. However, in Group 2 diffuse hepatic uptake was seen in 93 patients (97.9%) (p<0.05) and not seen only in 2 patients (2.1%). There is not a statistically significant relationship between the hepatic uptake and serum Tg, LT4 and TSH level. There is a statistically significant relationship between anti-Tg level and hepatic uptake. **Discussion:** Physiological diffuse hepatic uptake of radioiodine in WBS after RRA may not be seen during the early WBS. Thus, metastatic foci may be missed with early scanning. We conclude that RxWBS after RRA should be done in late period.

Keywords

Differentiated Thyroid Cancer; Radioiodine; Hepatic Uptake; Scintigraphy

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Introduction

Thyroid carcinoma is a rare malignancy, accounting for less than 1% of human malignant neoplasms. However, it is the most common endocrine malignancy and responsible for more deaths than all other endocrine cancers; however, the overall prognosis for patients with thyroid cancer is one of the best among all cancers [1]. Differentiated thyroid cancers (DTC), which include papillary and follicular cancer, comprise the vast majority (>90%) of all thyroid cancers [2]. The incidence shows a predominance in females. Total thyroidectomy is the primary treatment method for DTC. Postoperative radioiodine remnant ablation (RRA) is a routinely used treatment method at most institutions to destroy residual thyroid tissue and occult foci of neoplastic cells in DTC. Post-treatment whole-body scan (RxWBS) is recommended to assess disease staging and to document the RAI-avidity of any known or unknown structural disease after RRA or radioactive iodine treatment. Souza et al. [3] reported that RxWBS altered stage of disease in 8.3% of patients. Normal physiological uptake is seen in salivary glands, oropharynx, the stomach, the liver, the intestines, the urinary system, and the lactating breast tissue in RxWBS [4]. Intense hepatic uptake of iodinated thyroid hormone and thyroid hormone degradation products is usually seen when large treatment doses of ^{131}I are administered to patients. Diffuse homogenous hepatic uptake of ^{131}I on an RxWBS without visible uptake by the remnant or residual tumor suggests hidden metastases [2]. Furthermore, according to Nakayama et al. [5], increased hepatic uptake of ^{131}I on RxWBS may predict disease-related progression. It is thought that diffuse hepatic uptake of ^{131}I on RxWBS indicates that the liver metabolizes ^{131}I -labelled fragments of thyroglobulin secreted by the tumor [6].

The aims of this study were to investigate whether the hepatic visualisation after RRA showed the presence of metastatic or residual disease in patients with differentiated thyroid cancer and also to investigate whether early or late RxWBS had an effect on the physiological hepatic uptake.

Material and Method

This retrospective study was performed in accordance with the Helsinki Declaration. This study was approved by the local ethics committee. In this study 201 DTC patients were evaluated (152 female, 49 male, mean age: 49.61 ± 13 years, range: 18-85 years) who referred to our nuclear medicine department for high dose RRA between January 2016 and December 2017. Total thyroidectomy with or without cervical lymph node dissection was performed in all patients. All patients were instructed to follow a low-iodine diet for the 2 weeks prior to RRA. At least 4 weeks prior to RRA levothyroxine (LT4) withdrawal was used for TSH stimulation in all patients. Routine laboratory tests including serum thyroglobulin (Tg), anti-thyroglobulin antibody (anti-Tg Ab), thyroid stimulating hormone (TSH), and free-tetraiodothyronine (fT4) were measured on the day of treatment. On the second day after administration of ^{131}I , the patients resumed thyroid replacement therapy and a normal diet. The therapeutic ^{131}I dose ranged between 100 mCi and 200 mCi. RxWBS was done using a large field of view dual-head camera (QuantumCam™/DDD, Denmark) with high energy, parallel-hole

collimator, and photo peak was 364 keV with a 20% window. Continuous acquisition mode (anterior and posterior views) was used with a scanning ratio of 10 cm/s with 1024x512 matrix. RxWBS was performed earlier (in 1-4th day after RRA) in 106 patients (Group 1) and was performed later (in 5-9th day after RRA) in 95 patients (Group 2). Diffuse hepatic uptake of radioiodine were evaluated visually by two nuclear medicine specialists.

Statistical methods

SPSS 15.0 software was used for the statistical analysis. Relationship between hepatic uptake and timing of WBS was evaluated with Pearson's chi-squared test. T-test for two-independent samples or Mann-Whitney test were used to examine differences in ages, ^{131}I doses, serum Tg, anti-Tg Ab, fT4, and TSH levels between two groups. Significance level was presented as *p* value. It was assumed that the observed differences were statistically significant when the *p* value was less than 0.05.

Results

Patients' characteristics are given in Table 1. There were 152 females (75.6%) and 49 males (24.4%). Seventy patients (34.8%) were under 45 years of age, whereas 131 (65.2%) were 45 years and older. According to the histopathological results, 187 patients (93%) had papillary, 9 patients (4.5%) had follicular, 3 patients (1.5%) had well differentiated thyroid tumor of unknown malignant potential, 1 patient (0.5%) had hurthle cell carcinoma, and 1 patient (0.5%) had poorly differentiated thyroid carcinoma. The median value of the biggest tumor diameter was 15 mm (range (min-max): 2-90 mm). Median serum Tg level was 3.46 ng/ml (range (min-max): 0.01-776 ng/ml), median serum anti-Tg Ab level was 10 IU/ml (range (min-max): 0.001-866.6 IU/ml), median TSH level was 95.07 $\mu\text{IU/ml}$ (range (min-max): 8.55-240 $\mu\text{IU/ml}$), and median LT4 level was 0.17 $\mu\text{IU/ml}$ (range (min-max): 0.01-1.36 $\mu\text{IU/ml}$) when the RRA treatment was performed. Hepatic uptake was seen in 96 patients (47.8%) and there was no hepatic uptake in 105 patients (52.2%). In patients of Group 1, hepatic uptake were seen in only 3 patients (2.8%) and was not seen in 103 patients

Table 1. Demographic and clinico-histopathologic characteristics

Characteristics	n (%)
Age	
Mean \pm SD (range,min-max) (years old)	
49.61 \pm 13 years, (18-85 years)	
<45 years old	70 (34.8)
\geq 45 years old	131 (65.2)
Gender	
Female	152 (75.6)
Male	49 (24.4)
Pathological classification	
Papillary thyroid carcinoma	187 (93)
Follicular thyroid carcinoma	9 (4.5)
Well differentiated thyroid tumors of unknown malignant potential	3 (1.5)
Hurthle cell carcinoma	1 (0.5)
Poorly differentiated thyroid carcinoma	1 (0.5)

(97.2%) (Figure 1). In patients of Group 2, hepatic uptake was seen in 93 patients (97.9%) and not seen only in 2 patients (2.1%) ($p=0.0001$) (Figure 2) (Table 2). There was not a statistically significant relationship between the hepatic uptake and serum Tg, LT4, and TSH level ($p=0.241$, $p=0.092$, and $p=0.483$, respectively). Also there was not a statistically significant relationship between the hepatic uptake and given radioiodine dose and age ($p=0.161$ and $p=0.727$, respectively). There was a statistically significant relationship between anti-Tg level and hepatic uptake ($p=0.0001$). Of all patients, 14 patients had organ metastasis. Of those 14 patients, 7 patients had RxWBS at 1-4th day after RRA and only 1 patient had hepatic uptake. The other 7 patients had RxWBS at 5-7th day after RRA and 6 of them had hepatic uptake ($p<0.05$) (Table 3).

Discussion

RRA is an effective form of treatment that aims to decrease

cancer-specific mortality and recurrence after surgical treatment in patients with DTC. RxWBS is recommended several days after RRA. The optimal time for performing post-therapeutic scans to detect metastatic lesions is still controversial. Chong et al. [7] reported that post-treatment WBS done at 7th day after treatment is superior to post-treatment WBS done at 3rd day after treatment for diagnosing lung or bone metastasis. Salvatori et al. [8] stated that late scan is more informative than early scan and they found that patients who have normal findings at early RxWBS and pathologic findings at late RxWBS (thyroid remnants, lymph node, and distant metastasis) should be considered as high risk patients; synchronous high Tg levels were observed in these patients. Hung et al. [9] retrospectively analyzed the images of 239 patients who received 131I therapy and 3 sequential whole-body scans were performed on the 3-4th day, 5-6th day, and 10th-11th day after 131I administration. They found that 28% of lymph node metastases, 17% of lung

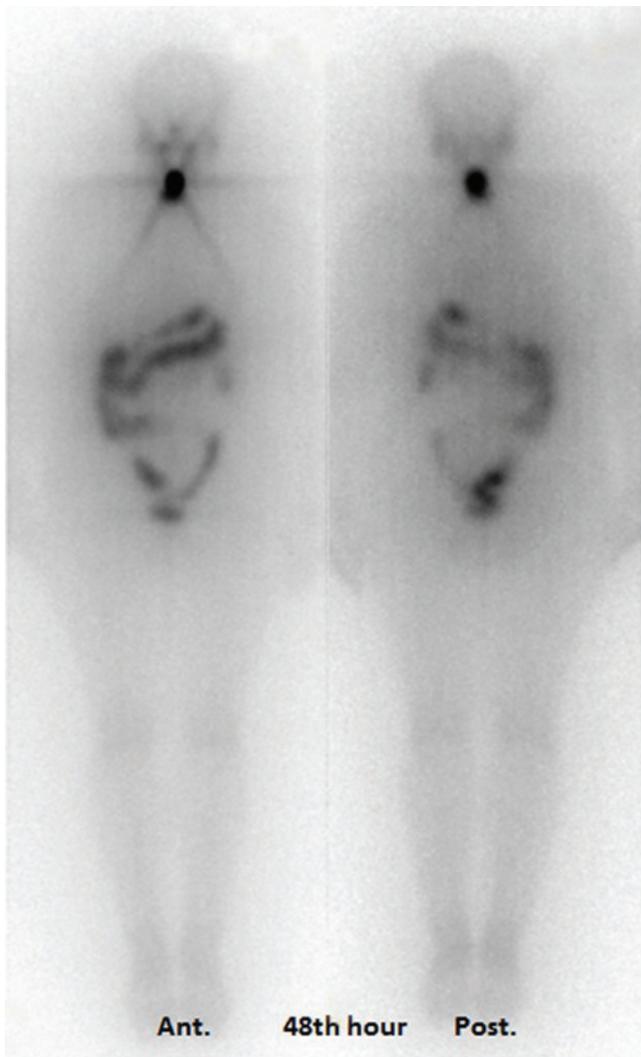


Figure 1. RxWBS at 1-4th day after RRA.

Table 2. Relationship between timing of WBS after RRA and hepatic uptake of 131I.

Time of WBS	Hepatic Uptake		Total	P value
	Present (%)	Absent (%)		
1-4th day	3 (2.8)	103 (97.2)	106	0.0001*
5-9th day	93 (97.9)	2 (2.1)	95	

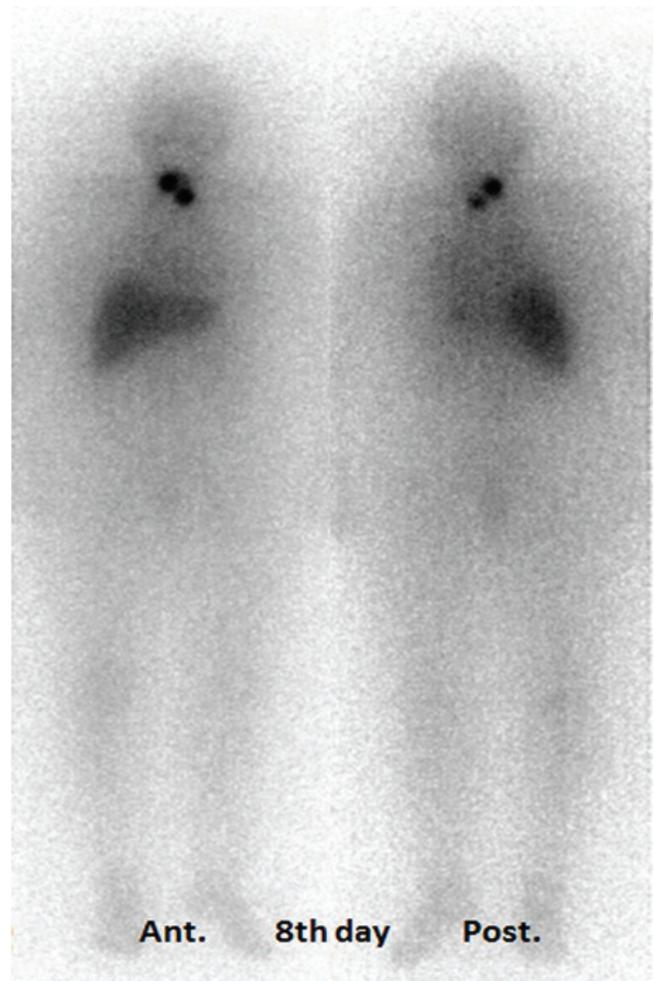


Figure 2. RxWBS at 5-9th day after RRA.

Table 3. Relationship between timing of WBS after RRA and hepatic uptake of 131I among the patients with organ metastasis.

	Organ Metastasis Present (%)	Hepatic Uptake of ¹³¹ I		P value
		Absent (%)		
Present	WBS at 1-4th day	1 (14.3)	6 (85.7)	0.008*
	WBS at 5-9th day	6 (85.7)	1 (14.3)	
Absent	WBS at 1-4th day	2 (2)	97 (98)	0.0001*
	WBS at 5-9th day	87 (98.9)	1 (1.1)	

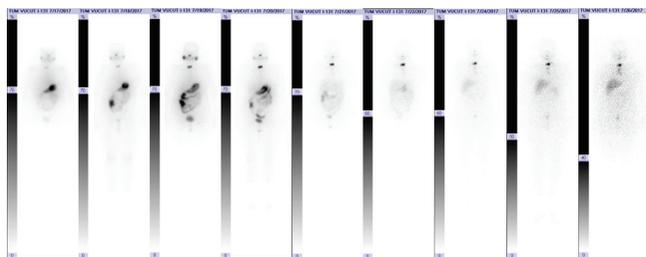


Figure 3. A patient scanned every day for 9 days after RRA. Initially, the amount of residual tissue appeared to be smaller, while the amount of true residual tissue was more clearly visible from day to day. Notice the hepatic uptake, which was not seen in the first days, began to be monitored from the 5th day with Tg/anti-Tg beginning to metabolize.

metastases, 16% of bone metastases and 5% of the remnants were missed on the late images performed at 10-11th day. They concluded that radioactive iodine remains for a shorter time in metastatic foci than in remnant tissue, and so metastatic foci may be missed when late scanning is performed. Approximately 80% of T4 is converted to T3 in the liver while the rest is conjugated with sulfate and glucuronide in the liver, excreted in bile, and partially hydrolyzed in the bowel. This is why diffuse hepatic uptake of ¹³¹I is seen on an WBS when radiolabeled T4 is released into the circulation from remnant thyroid tissues or residual tumor cells [11]. In our retrospective study, in Group 2, 93 of 95 patients had diffuse hepatic uptake, whereas in Group 1, only 3 of 106 patients had hepatic uptake on WBS. Of 14 patients with organ metastasis, 7 patients were in Group 1 and only 1 of those patients had hepatic uptake. The other 7 patients were in Group 2 and 6 of them had hepatic uptake. So we hypothesize that a late RxWBS is of serious importance for the patients with small undetectable residual/tumoral foci. Hepatic visualisation is an important marker of hormonal active residual thyroid tissue/tumoral tissue. And we may miss this important marker when RxWBS is performed earlier. Figure 3 shows the patient being scanned every day for 9 days. In the first days, the amount of residual tissue appeared to be smaller, but the amount of real residual tissue was increasing day by day. Also, the hepatic uptake, which was not seen in the first days, appeared from the 5th day, with Tg beginning to metabolize. There are different opinions about the clinical importance of diffuse hepatic uptake at RxWBS. Some clinicians report that hepatic uptake at RxWBS is a physiologic process whereas others emphasize that it shows there is residual thyroid tissue or metastatic foci in the body [10,12,13]. Chung et al. [12] reported that ¹³¹I labelled thyroglobulin may be secreted by thyroid tissue, and so liver uptake on RxWBS is related to the fraction of ¹³¹I labelled thyroglobulin in the serum. They found a positive correlation between diffuse hepatic uptake and ¹³¹I labelled thyroglobulin. In our study, although there was a statistical significance between hepatic uptake and presence of metastasis, no significant correlation was found between TG levels and hepatic uptake. Lee et al. [14] reported that the intensity of diffuse hepatic uptake on the late scan was significantly higher than that on the early scan. However, they reported that this was related to hepatic enzymes by showing the significant correlation with the serum levels of hepatic enzymes rather than the presence of thyroid remnants, metastatic DTC lesions, and tumor recurrence during follow-up. Omür et al. [15] showed that the lack of correlation between

hepatic radioactive iodine (RAI) uptake and Tg levels, functioning metastatic tissue, or thyroid remnants and they suggested that this may be related to factors other than thyroid tissue. Their study also showed positive correlation between administered RAI dose, hepatic enzymes, and hepatosteatosis. This correlation supports the conclusion that diffuse hepatic RAI uptake may be related to different mechanisms such as elevated hepatic enzymes, functioning metastatic tissue, or thyroid remnants, and Tg or anti-Tg levels. However, Tatar et al. [16] reported no significant association between liver uptake and uptake in the thyroid bed, dose of ¹³¹I administered for RRA, Tg levels, age, stage of the disease, local or distant metastases, recurrence, or survival. In our study there was not a statistically significant relationship between diffuse hepatic uptake and serum Tg, T4 levels, dose of radioactive iodine, presence of residual tissue, or presence of metastatic foci. However, there was a statistically significant relationship between anti-Tg level and hepatic uptake. In our study, patients were referred to our clinic at approximately 1 to 2 months after operation. At that time, there is a reaction against the Tg circulating in the body, resulting in the formation of anti-Tg. And a recent study done among 1126 PTC patients [17] concluded that positive thyroid auto-antibody status could be a risk factor for more metastatic cervical lymph nodes while also being a protective factor for distant metastatic disease in PTC patients.

Conclusion

Physiological diffuse hepatic uptake of radioiodine is mostly seen at late RxWBS and may be a sign for metastatic foci or residual thyroid tissue. Diffuse hepatic RAI uptake may be related to the presence of radiolabeled thyroglobulin fragments against the presence of metastatic tissue. Therefore we recommend that RxWBS should be performed in late period and metastatic or residual foci should be carefully researched with advanced imaging methods or close follow-up if no metastatic or residual foci were seen despite the presence of hepatic uptake at late RxWBS.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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