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Prevalence of Distant Metastases in Whole-Body Scan after Iodine Therapy in Low- and Intermediate-Risk Differentiated Thyroid Cancers

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ABSTRACT

Background and Objective: Differentiated Thyroid Cancer (DTC) is the most common endocrine malignancy with the fastest growing rate worldwide. The aim of this study is to investigate the prevalence of distant metastases in whole-body scans after iodine therapy in DTC patients with low and intermediate-risk and to evaluate its diagnostic role.

Methods: In this retrospective cohort study, patients with DTC who underwent total thyroidectomy and were referred for Radioiodine Remnant Ablation (RRA) to the nuclear medicine department of Shahid Beheshti Hospital were included in the study. According to ATA guidelines, patients were divided into two groups with low risk level (LR) and intermediate risk level (IR) and were evaluated for distant metastasis by whole-body scan after iodine treatment with a Single-Head Gamma Camera.

Findings: Out of 1039 patients included in the study, 149 (14.3%) were men and 890 (85.7%) were women. Thyroid remnant was present in whole-body scan after iodine treatment in 1030 patients (99.1%). Of these patients, 713 (68.6%) were in the LR group and 326 (31.4%) were in the IR group. The presence of cervical lymph node metastasis was detected in 69 people (LR:28, IR:41), mediastinal involvement in 11 people (LR:3, IR:8), lung metastases in 11 people, and bone metastasis in 3 people out of 101 patients. All of them were in the group of patients with intermediate risk. Multiorgan involvement was seen in 7 of 101 patients (LR:2, IR:5). The mean serum level of thyroglobulin (Tg) in cases of distant metastasis was 2.61±8.57 in the low risk group and 17.45±65.21 in the intermediate risk group, and these values showed statistically significant differences ($p<0.001$).

Conclusion: The results of the present study showed that the prevalence of distant metastases in whole-body scan after iodine therapy was seen in approximately 10% of patients. Serum thyroglobulin level can also be used as a clinical marker for early diagnosis of distant metastasis.

Keywords: *Differentiated Thyroid Carcinoma, Whole-Body Scan after Treatment, Radioactive Iodine Treatment, Residual Thyroid Tissue.*

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Introduction

In the last two decades, differentiated thyroid cancer (DTC) has become the most common endocrine malignancy with the fastest growing rate worldwide. Until a few years ago, the standard treatment for DTC consisted of total or near-total thyroidectomy followed by Radioiodine Remnant Ablation (RRA) and TSH suppressive therapy with levothyroxine (LT4) (1-3).

Based on the guidelines of the American Thyroid Association (ATA) in 2015, the initial risk level of patients with DTC was divided into three categories: low, intermediate and high, which was confirmed in several recent retrospective studies. In addition, this method of dividing the initial risk level was in accordance with the evidence that the mortality rate is very low in patients with low risk (LR) and intermediate risk (IR) levels (4-6).

The overall prognosis of DTC is 99.8% with a 5-year survival rate for local masses, 97% for masses with regional metastases, and 57.3% for masses with distant metastases (DM). Distant metastases are seen in 5-25% of patients, which are associated with a lower survival rate and require early and appropriate treatment to improve their prognosis. Lungs are the most common sites of distant metastases, followed by bones. Other rare cases include brain, liver and kidney (7). Distant metastases are seen in a small number of patients with DTC, but account for most of the disease-related mortality. Studies on the long-term outcome of patients with distant metastases are controversial (8).

The survival rate of patients with distant metastasis from DTC is significantly improved with iodine therapy after total thyroidectomy. Therefore, several courses of radioactive iodine treatment are often performed in these patients. A few days after iodine therapy, a post-treatment Whole-Body Scans (ptWBS) is performed to identify residual thyroid tissue or metastatic foci and to evaluate the uptake of known or unknown metastatic lesions (9). In recent years, there has been a trend to reduce the use of RRA to limit potential side effects, especially in patients with low-risk (LR) and intermediate-risk (IR) DTC, even though these side effects are insignificant for RAI doses less than 100 millicuries (10-12).

Today, there is general agreement that RRA should not be prescribed to patients with low-risk DTC (13, 14) unless a significant increase in disease-free survival or a reduction in mortality is demonstrated in these patients (15-19). In contrast, the use of RRA is recommended for high-risk patients, usually with high doses of radioactive iodine, in which this method has shown a positive effect on recurrence and survival (20, 21). The selective use of RRA is suggested for patients with intermediate risk, considering the level of risk of recurrence as well as the values of the serum level of thyroglobulin (Tg) after surgery and neck ultrasound (4, 22).

Despite the evidence of a limited therapeutic role of RRA in low- and intermediate-risk patients, to our knowledge iodine therapy is still widely used and only a few studies have been conducted regarding the benefit of the diagnostic role of ptWBS. Different results have been reported in several studies regarding the relationship between the initial risk level after total thyroidectomy, performing RRA and the prevalence of metastasis. Also, in some other studies, the risk of recurrence and stable disease increased with high levels of serum thyroglobulin after surgery (8, 22-25).

The aim of this study is to investigate the prevalence of distant metastases in ptWBS in differentiated thyroid cancers with low and intermediate risk levels and to evaluate the diagnostic role of ptWBS so that it can be used in the treatment strategies of patients.

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Methods

After being approved by the ethics committee of Babol University of Medical Sciences with the code IR.MUBABOL.HRI.REC.1402.089, this retrospective cohort study was conducted on patients with DTC who were treated with total thyroidectomy and referred to the Nuclear Medicine Department of Shahid Beheshti Hospital in Babol for RRA. According to TNM and ATA guidelines, low-risk (LR) patients including T1-2mN0/xM0/x and intermediate-risk (IR) patients including T1-3N1Mx and T3N0Mx patients were included in the study. Patients who are at high risk level were excluded from the study.

For radioactive iodine treatment, levothyroxine (LT4) tablets were discontinued in all patients for at least 3 to 4 weeks in order to increase TSH above 30 mU/L. According to the standard guidelines, radioactive iodine was administered from 30 to 175 millicuries according to the physician's opinion, and then a whole-body scan (ptWBS) was performed from 3 to 7 days after iodine treatment. Neck ultrasound, serum thyroglobulin, and thyroid hormone measurements were performed in all patients. To avoid misinterpretation of thyroglobulin measurements, all patients were screened for circulating anti-thyroglobulin antibodies. Doppler ultrasound of the neck was performed in all patients before RRA. The thyroid region and the central, laterocervical and supraclavicular regions were examined for recurrence or continuation of the suspected disease. In suspected lymph node metastases, aspiration biopsy was performed with ultrasound guidance.

Whole-body scanning after iodine treatment was performed using a Single-Head Gamma Camera with large field of view (SIEMENS Orbiter 75 ZLC) equipped with high energy and high-resolution beam generator. After collecting the data, they were entered into SPSS software version 24 and were analyzed with descriptive indices including mean, standard deviation, average ranks, frequency and percentage, and Mann-Whitney and Kruskal-Wallis tests, and $p<0.05$ was considered significant.

Results

A total of 1039 patients were included in the study, of which 149 (14.3%) were men and 890 (85.7%) were women. The mean age of patients participating in this research was 40.3±11.3 (from 14 to 82 years old) (Table 1). The thyroid remnant in ptWBS was not seen in 9 patients and was present in 1030 patients (99.1%). Of these patients, 713 (68.6%) were in the LR group and 326 (31.4%) were in the IR group. Moreover, ptWBS showed abnormal areas of absorption of radioactive iodine (I^{131}) in other parts of the body in 101 patients (9.7%), and abnormal findings of absorption were not seen in the scan in 938 patients. Patients were divided into five groups based on the received dose of radioactive iodine: 30, 100, 125, 150 and 175 millicuries. LR patients received doses of 30, 100 and 125 and IR patients received doses of 150 and 175 millicuries for treatment.

Table 1. Demographic characteristics of the studied patients (n=1039)

Thyroid scan findings	Number(%)
Gender	
Woman	890(85.7)
Man	149(14.3)
Level of risk	
Low	713(68.6)
Intermediate	326(31.4)
Thyroid remnant in whole-body scan after iodine therapy	1030(99.1)
Patients with abnormal areas of iodine uptake	101(9.7)
Patients without abnormal areas of iodine uptake	938(90.3)

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Cervical lymph node metastasis was present in 69 of 101 patients (LR:28, IR:41), mediastinal involvement in 11 of 101 patients (LR:3, IR:8), lung metastases in 11 of 101 patients, and bone metastasis was seen in 3 out of 101 patients, all of which were in the group of patients with an intermediate risk level (Table 2). Multi-organ involvement (including lung, mediastinal lymph nodes and bone) was seen in 7 of 101 patients (LR:2, IR:5).

47 of 69 cervical lymph node metastases were also detected by neck ultrasound and confirmed by fine needle aspiration cytology. Out of the remaining 22 cases, 13 were reported with metastatic involvement in ultrasound. In the other 9 cases, abnormal cervical uptake was seen only in the whole-body scan after treatment, which was considered as cervical lymph node metastasis after ruling out other possibilities such as contamination, artifact, etc. 7 out of 11 mediastinal lymph node metastases were also detected by chest CT scan with injection and reported as metastatic involvement. In the other 4 cases, they were seen only in the post-treatment whole-body scan.

Table 2. Frequencies of sites of involvement and abnormal absorption of patients based on initial risk level

Involved organ	Low risk Number(%)	Intermediate risk Number(%)	Total
Cervical lymph nodes	28(40.57)	41(59.43)	69
Mediastinal lymph node	3(27.27)	8(72.73)	11
Lung	0(0)	11(100)	11
Bone	0(0)	3(100)	3
Multi-organ	2(28.57)	5(71.43)	7
Total	33(32.67)	68(67.33)	101

All 11 cases of pulmonary metastases were detected by CT scan of the lungs and reported as metastatic involvement. All 3 cases of bone metastases were detected in the whole-body scan after treatment (involved areas including thoracic vertebrae, skull, pelvis and femur) in plain radiography. In 2 of these patients, where bone scans were performed later, in one case, more metastatic lesions were observed in the skeletal system than in whole-body scans after iodine therapy. In 7 of 101 patients, multiorgan metastatic involvement was seen in ptWBS.

The mean serum level of thyroglobulin after discontinuation of levothyroxine during iodine treatment, which can be considered as post-surgery control, was investigated in two groups (Table 3). The mean serum level in the LR group was 2.61±8.57 ng/ml (range of 0.04-223) and 17.45±21.65 ng/ml in the IR group (range of 0.2-700 ng/ml); the difference between the two groups was statistically significant ($p<0.001$). The mean serum level of thyroglobulin after stopping levothyroxine tablets during iodine therapy, in the group without abnormal absorption in whole-body scan after treatment was 2.84±2.33 ng/ml (range of 0.04-16 ng/ml) and it was 48.54±113.69 ng/ml in the group with abnormal absorption (range of 0.7-700 ng/ml); the difference between the two groups was statistically significant ($p<0.001$).

Table 3. Mean serum thyroglobulin level after discontinuation of levothyroxine during iodine treatment

Patients	Mean±SD (ng/mL)	Average ratings	Range (ng/mL)	p-value (Man-Whitney test)
Low risk	2.61±8.57	406.4	0.04-223	<0.001
Intermediate risk	17.45±65.21	767.35	0.2-700	<0.001
No abnormal areas of iodine absorption	2.84±2.33	478.68	0.04-16	<0.001
With abnormal areas of iodine absorption	48.54±113.69	903.72	0.7-700	<0.001

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The mean serum level of thyroglobulin in groups with abnormal uptake in ptWBS in the cervical lymph node metastasis group was 8.7±5.2 (range of 0.7-25 ng/ml), in the mediastinal lymph node metastasis group was 19.4±9.6 (range of 10-43 ng/ml), in lung metastasis group was 223.7±180.7 (range of 36-500 ng/ml), in bone metastasis group was 141.3±60.4 (range of 93-209 ng/ml) and in the group with multiple organ involvement was 172.5±247 (range of 6.6-700 ng/ml) (Table 4). In the comparison of the mean serum level of thyroglobulin in the groups with abnormal uptake in ptWBS, there was a significant difference between the cervical and mediastinal lymph node metastasis groups with other involved groups ($p<0.001$). But there was no significant difference between other involved groups, including lung, bone and multi-organ metastasis.

Table 4. The mean serum level of thyroglobulin after discontinuation of levothyroxine tablets in groups with abnormal areas of iodine absorption

Involved organ	Mean±SD (ng/mL)	Average ratings	Range (ng/mL)	p-value (Kruskal-Wallis test)
Cervical lymph nodes	8.7±5.2	37.05	0.7-25	<0.001
Mediastinal lymph node	19.4±9.6	68.68	10-43	<0.001
Lung	223.7±180.7	92.32	36-500	<0.001
Bone	141.3±60.4	91.33	93-209	<0.001
Multi-organ	172.5±247	78.5	6.6-700	<0.001
Total	48.54±113.69	-	0.04-700	<0.001

At the end of follow-up (median of 7.5 years), 76 of 101 patients with positive ptWBS were free of disease (LR:32, IR:44). While the other 25 patients had stable disease (LR:1, IR:24) with no difference in outcome according to baseline risk level. Of the 25 cases with stable disease, 7 cases had "biochemical" disease and 18 cases had "structural" disease (1 case of cervical lymph nodes, 1 case of mediastinal lymph nodes, 7 cases of lung involvement, 6 cases of multiorgan involvement, and 3 cases of bone involvement) (Figure 1). Moreover, by the end of the follow-up period, 10 of 101 patients with metastatic involvement died (3 cases of lung involvement, 4 cases of multi-organ involvement, and all 3 cases of bone involvement). 76 of 101 patients who were disease-free during follow-up showed this result in 41 cases (LR:38, IR:3) after a course of treatment with I^{131}, and in 39 cases (LR:12, IR:37), after several courses of treatment with iodine-I^{131} or other treatment methods (alcohol injection, radio frequency treatment and radiation therapy). In addition, 49 patients (LR:30, IR:19) underwent re-surgery (one or more times).

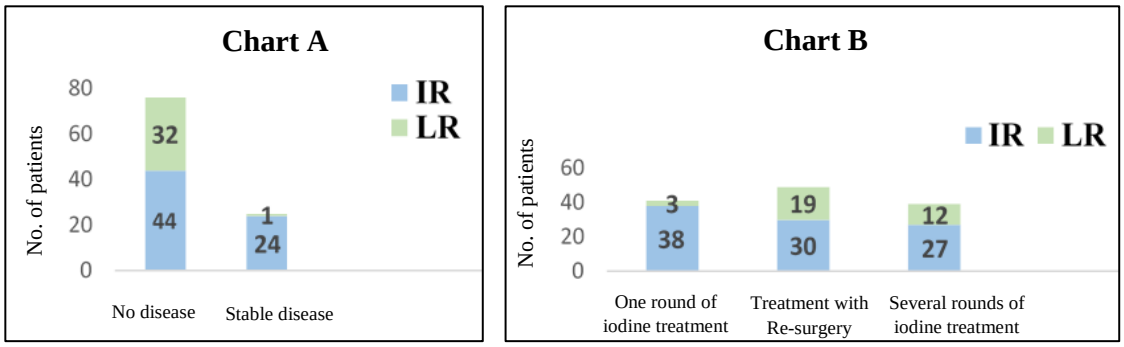


Figure 1. Chart A: Results of LR and IR patients with abnormal extrathyroidal absorption in ptWBS after the end of follow-up, Chart B: Treatment methods used to achieve recovery in LR and IR patients with abnormal extrathyroidal absorption in ptWBS

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Discussion

In our study, the prevalence of distant metastases in the whole-body scan after iodine therapy was approximately 10% of patients. Serum thyroglobulin level can also be used as a clinical marker for early diagnosis of distant metastasis. Today, physicians are faced with an increasing number of patients with DTC in LR and IR groups, and there is a need for safe, efficient, and cost-effective management strategies to avoid overtreatment and maintain quality of life. Despite the fact that RRA has traditionally been a cornerstone of DTC treatment, the decision to use RRA in LR and IR patients is more controversial (25). ptWBS is routinely used to confirm the site of uptake after RRA treatment and helps to detect physiological accumulation in the remaining thyroid tissue and pathological accumulation in lymph nodes in the neck, upper mediastinum, lung and bone (26).

Few studies have been published on the diagnostic role of RRA, which is related to the higher sensitivity of ptWBS in finding metastases not detected by other imaging methods.

In the present study, we analyzed ptWBS outcomes in 712 LR patients and 327 IR patients treated with different doses of I^{131} for RRA after levothyroxine (LT4) discontinuation. Also, in this study, ptWBS had a diagnostic role in approximately 10% of patients after RRA because it identified local or distant metastases in this group of patients. In addition, thyroid remnant was present in most cases (99%), and ptWBS showed the presence of metastasis to cervical lymph nodes in 69 cases (6.6%), metastasis to mediastinal lymph nodes in 11 cases (1.1%), pulmonary metastases in 11 cases (1.1%), bone metastases in 3 cases (0.3%), and multi-organ involvement in 7 cases (0.7%). In the present study, approximately 10% of patients treated with RRA had pathologic masses considered as lymph nodes or distant metastases, which was more than the study of Agate et al. (less than 2%) and less than the study of Iwano et al. (28%) (25, 26).

In cases of cervical lymph node metastases, 47 out of 69 cases were diagnosed by neck ultrasound and confirmed by cytology examination, and 13 other cases were reported with a view suggesting metastatic involvement, which were candidates for treatment or under follow-up without performing cytological examination. Therefore, the diagnostic role of ptWBS in cases of cervical metastasis was limited to only 9 patients. Similar to the study of Agate et al., the high accuracy of neck ultrasound for identifying metastatic neck lesions was also confirmed in our study (25).

Of the remaining 32 cases, 11 had mediastinal lymph node metastases, 11 had lung metastases, 3 had bone metastases, and 7 had multiorgan involvement, all of which might not have been detected without the use of ptWBS. Among these 32 cases, 5 were LR patients, 27 were IR patients, of which only 3 cases showed a more aggressive histological variant. This finding may indicate a decrease in the prognostic importance of the risk level in predicting the presence of metastatic lesions outside the neck.

In our study, the rate of lung and bone metastasis was 1.1% and 0.3%, respectively, which was significantly lower compared to the study conducted in Brazil by Couto et al. (24). The rates of pulmonary and bone metastatic involvement in their study were 14.3% and 4.4%, respectively, and this difference was due to the selection of patients with a high-risk level, while we examined patients with a low and intermediate risk level. In our study, as in their study, there was a significant difference in thyroglobulin levels between patients with and without metastasis.

In a study by Carlos et al., 6.7% of patients had distant metastases, and the most involved organs were lungs and bones (8), which is 3% in our study. Perhaps the two-fold difference is because in the study by Carlos et al., patients were not categorized according to risk level (8).

In the study of Agate et al., there was no special relationship between thyroglobulin serum level and distant metastases, and it was shown that only in cases of pulmonary metastases, thyroglobulin levels above 100 ng/ml can raise suspicion and prompt the physician to perform other diagnostic imaging tests or perform RRA and ptWBS (25). But in our study, there was a significant relationship between thyroglobulin serum

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levels and distant metastases ($p<0.001$). This finding can indicate the importance of thyroglobulin serum levels in the suspicion of distant metastases, so that in high thyroglobulin levels, performing additional imaging seems logical. Also, unlike the study of Agate et al., who did not find any difference according to the initial risk level (25), there was a significant difference between these two groups, LR and IR in our study. Perhaps the reason for this difference was the lower level of metastatic involvement in their study (less than 2%).

Moreover, in the present study, 60 cases out of 69 patients with metastatic lymph node involvement in the neck were diagnosed by ultrasound, who were treated because of this finding, but in the remaining 9 cases of cervical lymph node metastasis and in all cases of mediastinal, lung, and bone metastasis, the cost-effectiveness of RRA and ptWBS has been revealed in all LR and IR patients. In conclusion, maybe the diagnostic role of ptWBS in LR and IR patients who were prepared with LT4 discontinuation is important and related to treatment strategies.

It is not possible to comment with certainty what the outcome of these cases would have been if ptWBS had not been performed, although most of them may have been eventually treated with appropriate treatment strategies, and it is not possible to determine precisely what the outcome would have been if metastatic lesions had been detected later. However, it seems that by detecting the distant metastatic involvements diagnosed in ptWBS as soon as possible and using the appropriate treatment strategy, we can hope for a significant improvement in these patients.

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