



Retrospective Evaluation of Radioactive Iodine Ablation Therapy in the Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features (NIFTP) And Thyroid Tumors With Uncertain Malignity Potential

Mehmet Refik GOKTUG¹, Ozen OZ GUL¹, Soner CANDER¹

¹Mus State Hospital, Department of Internal Medicine, Mus, Turkey

¹Bursa Uludag University Faculty of Medicine, Division of Endocrinology and Metabolic Diseases, Bursa, Turkey

ABSTRACT

Background Noninvasive Follicular Thyroid Neoplasm (NIFTP), Well differentiated thyroid tumor with uncertain malignity potential (WDT-UMP), follicular thyroid tumor with uncertain malignity potential (FT-UMP), and Hurtle cell neoplasia with uncertain malignity potential (HCN-UMP) have been included in the classification of thyroid tumors by WHO, with the incidence of thyroid cancer increasing every passing year. There is no consensus regarding the follow-up and treatment processes of these tumors. Our study aims to shed light on our clinical practice by evaluating the follow-up processes of the groups with and without radioactive iodine ablation in patients followed up with these diagnoses.

Material and Methods The 49 patients older than 18 years of age and followed for at least 12 months, who were performed subtotal and total thyroidectomy between 2015 and 2020 and were diagnosed with WDT-UMP, FT-UMP, HCN-UMP, and NIFTP according to histopathological examination were included to the study.

Results Tumor type rates did not differ between the groups that received and did not receive RAI treatment ($p=0.361$). The mean follow-up period did not differ between the groups that received and did not receive RAI treatment. Also the rates of RAI treatment according to tumor size did not differ ($p=0.413$). Tumor size was larger than 4 cm in 13 patients, and 1 patient from this group had received RAI treatment. Recurrence was not detected in the 49 patients included in our study who received or not receive RAI treatment.

Conclusions Some studies recommend giving RAI to these borderline thyroid tumors larger than 4 cm. But in our study no recurrence was detected in patients who did not receive RAI. That supports the view that patients could be followed without RAI treatment even if they are large tumors.

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Keywords: Noninvasive Follicular Thyroid Neoplasm (NIFTP), Well differentiated thyroid tumor with uncertain malignity potential (WDT-UMP), follicular thyroid tumor with uncertain malignity potential (FT-UMP), Hurtle cell neoplasia with uncertain malignity potential (HCN-UMP), RAI ablation, recurrence.



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Address for Correspondence:

Mehmet Refik Goktug, MD

Mus State Hospital, Department of Internal Medicine,
Mus, Turkey

E-mail: mrgoktug@hotmail.com



Introduction

Thyroid cancers are the most common endocrine organ cancer.¹ It constitutes approximately 2.3% of newly diagnosed cancers all over the world.² It is the second most common cancer in women after breast cancer in Turkey, and it is seen approximately four times more frequently in women than in men.³ There has been an increase in the incidence of thyroid cancers in the last three decades. With the increasing incidence of thyroid cancer each year, in addition to classical type differentiated thyroid cancers, an increase is observed in atypical thyroid tumors whose malignant potential is not fully determined.⁴ Thereupon, the classification of thyroid tumors was revised in 2017 by WHO. Non-invasive papillary tumor features of follicular tumors (NIFTP), well-differentiated tumor with uncertain malignant potential (WDT-UMP), follicular tumor with uncertain malignant potential (FT-UMP), and Hurthle cell tumor with uncertain malignant potential (HCN-UMP) are included in the new classification.⁴

There are differences of opinion on how to manage the follow-up processes of these borderline tumors. Some researchers have stated that the evaluation of these tumors as carcinoma did harm more than benefit, resulting in treatment methods such as overtreatment, unnecessary total thyroidectomy, radioactive iodine ablation therapy, and suppression of TSH levels with levothyroxine is used.⁵

We aimed to light on our clinical practice by evaluating the results of the groups with and without radioactive iodine ablation in patients followed up with the diagnoses of NIFTP, WDT-UMP, FT-UMP, and HCN-UMP.

Material and Methods

Study Protocol

Our study has planned to evaluate the retrospective and cross-sectional data of patients followed up in our endocrinology outpatient clinic with the diagnoses of WDT-UMP, FT-UMP, HCN-UMP, and NIFTP. This study was carried out following the Helsinki Declaration decisions, the Patient Rights Regulation, and ethical rules. The study started after the local ethics committee

approval was obtained with the decision dated 14 July 2022 and numbered 2020-1/17.

The files of 53 patients who underwent subtotal and total thyroidectomy between 2015 and 2020 were diagnosed with WDT-UMP, FT-UMP, HCN-UMP, and NIFTP according to histopathological examination were analyzed. Inclusion criteria were over 18 years of age, followed for more than 12 months, no concomitant papillary carcinoma. One patient was younger than 18, two patients were applied less than 12 months, and one patient had papillary thyroid carcinoma with the current diagnosis. The information was reviewed of the patients retrospectively from archive records and electronic media files in the hospital automation system. In detail, were examined the treatments and follow-up processes applied to the patients.

Statistical Analysis

The conformity of continuous variables to the normal distribution was examined using the Shapiro-Wilk test. According to the test results, the variables were expressed as mean \pm standard deviation or median (minimum: maximum) values according to the results they were suitable. Categorical variables are given with numbers and percentages. Intergroup comparisons of continuous variables were made using the t-test for independent pair samples. Categorical variables between groups were compared using Fisher-Freeman-Halton and Fisher's chi-square tests. SPSS for statistical analysis (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used, and type I error level was accepted as 5% in statistical analysis.

Results

A total of 47 patients were included in the study. While the mean total follow-up period was 33 months in patients who received RAI, it was 30 weeks in patients who did not receive RAI ($p=0.266$). Of eight patients who underwent RAI, two (25%) had WDT-UMP, three (37.5%) FT-UMP and three had (37.5%) NIFTP. In the RAI non-received group, WDT-UMP was present in 13 patients (33.3%), FT-UMP in 12 patients (30.8%), NIFTP in 6 patients (15.4%), and HCN-UMP in 8

Table 1. Comparison of pathological diagnosis rates and follow-up time between groups that received and did not receive RAI treatment.

| | RAI (n=8) | Non-RAI (n=39) | p value |
|------------------------|------------|----------------|--------------------|
| Pathological diagnosis | | | 0.361 ^a |
| WDT-UMP | 2 (25%) | 13 (33.30%) | |
| FT-UMP | 3 (37.50%) | 12 (30.80%) | |
| NIFTP | 3 (37.50%) | 6 (15.40%) | |
| HCN-UMP | 0 | 8 (20.50%) | |
| Tracking time (months) | 33.63±4.84 | 30.49±7.53 | 0.266 ^b |
| Recurrent disease | 0 | 0 | |
| Tumor size* | | | 0.413 ^c |
| <4 cm | 7 (20.60%) | 27 (79.40%) | |
| ≥4 cm | 1 (7.70%) | 12 (92.30%) | |

Data were expressed as median (minimum:maximum) and n (%).

* Relevant percentage values were calculated according to tumor size variable.

a: Fisher-Freeman-Halton test, b: t-Test for independent samples, c: Fisher's Exact Chi-square test.

patients (20.5%). The tumor was larger than 4 cm in 1 (12.5%) of the patients who received RAI and in 12 (30.7%) of the patients who did not receive RAI (Table 1).

The rates of pathological tumor types did not differ between the RAI and non-RAI groups ($p=0.361$). WDT-UMP and NIFTP diagnoses were observed at the highest rate in the RAI group (37.5%); WDT-UMP (33,30) and FT-UMP (30.8%) diagnoses were observed at the highest rate in the non-RAI received group (37.5%). In addition, it was determined that the mean follow-up period did not differ between the groups that received and not received RAI treatment. No signs of recurrence were detected in any of the patients who had or had not undergone RAI. Therefore, it was thought that RAI treatment had no effect on recurrence in these tumors with uncertain malignant potential, since no recurrent tumors were detected in patients who received or did not receive RAI treatment, regardless of tumor size and type.

Discussion

In this study; The RAI treatments of the patients followed in our hospital with the diagnoses of WDT-UMP, FT-UMP, HCN-UMP, and NIFTP were evaluated. In the comparison of the treatment modalities and follow-up processes of these four groups, no statistically significant difference was found between them, and no recurrence were detected in any of the patients who had or had not undergone RAI ablation therapy.

After the diagnosis of NIFTP started to be used, to these patients could be reached no consensus on giving RAI treatment. Although some studies suggest that RAI treatment is not needed in tumors <4 cm, but RAI treatment can be given in tumors ≥4 cm, there is no consensus.

In the study reported by Capucine Richard et al.⁶ histopathological preparations of patients with PTC between 1975 and 2015 were re-examined, and 65 of these patients

were diagnosed with NIFTP. If this patient's was performed examination was 50 total thyroidectomy and 15 lobectomies, 45 (70.8%) RAI treatment. In the study reported by [Bin Xu et al.](#)⁷, follow-up periods ranged from 1.9 to 27.3 years after the first treatment, and it was reported that all patients remained in complete remission during follow-up. The mean tumor size was 4.5 cm in 79 patients included in the study, in which NIFTP patients with a nodule diameter of ≥ 4 cm showed long-term follow-up results. There are 32 patients with a clinical follow-up of 2 years or more and who did not receive RAI treatment. No disease was observed in the patients in this group during the follow-up period. In our study, 7 of 10 patients had a tumor size of < 4 cm and 3 of 10 patients was given RAI treatment. All those receiving RAI treatment had concomitant micropapillary carcinoma. Tumor size was > 4 cm in 1 of the patients who received RAI treatment. No relapse was observed in any patient during the follow-up period. These data support that the malignant potential of tumors is very low and these patients have not required post-operative RAI treatment.

There is no established protocol for the treatment and follow-up management of WDT-UMP due to their unknown biological behavior to date. There was no consensus on the treatment of lobectomy, total thyroidectomy, and RAI in the treatment of this patient. The general view is that this group of tumors has a good prognosis and is very low recurrence rate. [Lie et al.](#)⁵ stated that no recurrence was found during the 80-month follow-up of 20 WDT-UMP cases with follow-up data. In another study by [Adela Nechifor-Boila et al.](#)⁸, 21 cases were taken from the four follower route and gave disease and recurrence. The mean follow-up period of the 15 WDT-UMP patients included in our study was $33.63 \pm 4.84.2$ months of these patients had received RAI treatment, and the remaining 13 patients did not receive RAI treatment. Recurrence was not observed in any of the patients.

As in NIFTP and WDT-UMP, there is no consensus on the treatment and follow-up processes in patients with FT-UMP. It has been stated that RAI treatment could be considered

in tumors with a diameter of ≥ 4 cm since they are tumors with very low malignanc potential. In the literature review, no study was found showing the treatment and follow-up results of patients with FT-UMP. In our study, 3 of the 15 patients followed up with FT-UMP were given RAI treatment, while the other patients were not. There were 2 patients with tumor size ≥ 4 cm, and two of them were not given RAI treatment. The mean follow-up period of the patients was 31.1 months. No recurrent disease was detected in the patients during the follow-up period. The data in our study support the view that FT-UMP, which has a very low malignancy potential, could be followed without RAI treatment.

Hurtle cell thyroid carcinoma all differentiated thyroid, It constitutes less than 5% of malignancies. It is of follicular cell origin, and its biological behavior differs from other thyroid cancer histologic. Minimally invasive, It can be classified as Hurtle cell carcinoma and widely invasive hurtle cell thyroid carcinoma. However, in recent studies, it has been reported that there are cases of hurtle cell carcinoma with uncertain malignant potential and that it should be added to the classification.⁹ There are case reports supporting this in the literature. However, there is no study reporting post RAI treatment follow-up results of these patients in our knowledge. [Christopher Juhlin et al.](#)⁹ published a case report on HCN-UMP. In this case, is presented a 50-year-old male patient. Tumor size was 30 mm in the operative pathology, RAI was not recommended to the patient, and no recurrence tumor was detected in the 4-month follow-up of the patient. In our study, there were 8 patients followed up with HCN-UMP. The patients followed up with HCN-UMP RAI was not applied to RAI. The mean follow-up period of the patients was 29.3 months, and no recurrence was observed in any of the patients.

Conclusions

As a result, in the literature since there is no study evaluating the radioactive iodine ablation treatment of all thyroid tumors in our country, our study is the first national study in this field. Of the 49 patients included in our study, 8 received RAI treatment, 41 did not, and none of them relapsed. The disease was not detected tumor size was large than 4 cm in 13 patients, and only one patient from this group had received RAI treatment. This supports the view that patients can be followed without RAI treatment in even large tumors, and it is thought that our study will contribute to the literature in this regard.

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: MRG; Study Design: OOG, SC; Supervision: OOG, SC; Materials: MRG; Data Collection and/or Processing: MRG; Statistical Analysis and/or Data Interpretation: MRG, OOG, SC; Literature Review: MRG, OOG, SC; Manuscript Preparation: MRG, OOG, SC; Critical Review: OOG, SC.

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