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# Is the Multifocality Rate in Thyroid Cancer Patients Increasing Over the Years

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**ABSTRACT**

Papillary thyroid cancer (PTC) is the most common type of thyroid cancer, and its incidence continues to increase. Multifocality is common in PTC, and it has been suggested in many studies that multifocality may be associated with poor prognosis. In this study, data of patients followed with multifocal PTC were evaluated.

Following the approval of the local ethics committee, the data of patients who received total thyroidectomy and subsequent radioactive iodine (RAI) treatment for thyroid cancer between 2012 and 2020 were evaluated.

Multifocality was detected in 142 (19.88%) of the 714 PTC patients studied. The rate of multifocality among PTC patients was 3.29% in 2012, 7.2% in 2013, 10.1% in 2014, 10.5% in 2015, 38.15% in 2016, 31.6% in 2017, 33.33% in 2018, 32.58% in 2019 and 22.22% in 2020. Of these patients, 52.1% had 2 foci, 20.4% had 3 foci, 15.5% had 4 foci, and 12% had 5 or more foci. Multifocality was observed in the right and left lobe in 54.2% of the patients, the right lobe in 21.1% of the patients and the left lobe in 12.7% of the patients. Multifocality was not detected in the isthmus only. It was found that as the number of tumor foci increased, differentiation decreased. It was observed that multifocality was more common in microcarcinomas.

In our clinic, it has been observed that the rate of multifocal PTC has increased in recent years. This significant increase may be the result of morphological changes as well as improvements in diagnosis and treatment.

**Keywords:** Papillary thyroid cancer; Rradioactive iodine; Multifocality; Differentiation; Thyroid

## Introduction

The incidence of thyroid cancers continues to increase rapidly, but the mortality rate has remained stable. According to GLOBOCAN data, thyroid cancers are the 5th most common type of cancer in women (4.9%) (1). Papillary thyroid carcinoma (PTC) is the most common thyroid cancer and constitutes approximately 80% of the cases (2). Multifocality is frequently observed in PTC, and it has been reported in different studies that it can be detected in 20 to 36% of patients (3-5. 50 to 70% of multifocal thyroid cancers are bilateral (6). The reason for multifocality is attributed to two hypotheses: The first is that intrathyroidal metastasis can cause multifocality. It is predicted that multifocal tumors due to this mechanism have a more aggressive course. The second proposed mechanism of multifocality is primary tumors that occur simultaneously in the thyroid gland (7).

Although it is claimed that PTC progresses slowly, some clinicopathological subtypes are reported to have a more aggressive course. Many factors are affecting the prognosis in PTC such as age, gender, stage and histopathological features (8). Some researchers have reported that multifocality and bilaterality are important factors in disease progression and increase the risk of recurrence in PTC, and they recommended a more aggressive treatment approach for such patients (2,9). However, multifocality and bilaterality are not included in the current thyroid cancer staging guidelines (10,11).

Multifocality in PTC can usually be detected as a result of a comprehensive pathological examination of the resected thyroid gland, but it is often not detected preoperatively (12). Therefore, in the treatment strategy of patients with suspected malignancy, total thyroidectomy is applied in many clinics with the thought that partial thyroidectomy may give rise to reoperations. However, there may be some differences in clinical practice.

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Many studies have been done on multifocality in PTC. There are many uncertain issues associated with clinicopathological and prognostic factors of thyroid cancer patients, and uncertainties persist in the PTC treatment. This single-center retrospective study evaluated the distribution of PTC patients over the years and evaluated clinicopathological data of PTC patients who received radioactive iodine (RAI) treatment between 2012-2020.

RAI therapy has been recognized as targeted therapy with limited side effects for PTC due to the thyroid gland's affinity for iodine. After total thyroidectomy, with RAI treatment, residual normal thyroid tissue and suspicious metastases can be treated. This treatment method provides increased disease-free survival (13). Therefore, the use of RAI treatment has increased today (14).

## Material and Methods

**Patients:** Our single-center study was conducted with the approval of the Local Clinical Research Ethics Committee. 714 PTC patients who underwent total thyroidectomy and then received RAI ablation therapy between 2012 and 2020 were included in this study. Patients with any of the following factors were excluded from the study: [1] those without PTC (medullary/follicular/anaplastic thyroid carcinoma patients); [2] those undergoing non-curative thyroid surgery; [3] those who could not be followed up after surgery.

**Radioactive iodine treatment and whole-body scanning protocol:** In all patients, thyroid hormone replacement therapy was discontinued for at least 4 weeks before RAI treatment with I-131, and an iodine-poor diet was administered in the last 10 days before treatment. Anterior and posterior whole-body scintigraphy (TxWBS) was performed between 3 and 8 days after RAI treatment. A high-energy parallel hole collimator was used in a double-headed gamma camera (DDD-QuantumCam) for whole-body scintigraphy (364 kEv-% 20 energy window-7cm/min). Levothyroxine replacement therapy was initiated in all patients after RAI treatment. Clinical, radiological, and laboratory data of the patients included in the study both during the ablation treatment and during the post-treatment follow-up were recorded. For clinical follow-up, physical examination and neck ultrasonography were performed and serum Tg, anti-TgAb, TSH levels were measured. Data of patients who underwent diagnostic whole-body scan (DxWBS) with low dose I-131 between 8 and 10 months after RAI treatment were recorded. Patients with serum Tg levels too low to be detectable (stimulated Tg <1 ng/ml) while TSH was stimulated, or patients with non-stimulated Tg <0.2 ng/ml; patients without radiological and clinical findings consistent with lymph node or distant metastasis; patients with no pathological findings in DxWBS with low dose I-131 between 8-12 months after RAI treatment were considered successful ablation.

**Statistical Analysis:** Statistical analyses were performed using the SPSS software version 23 (Statistical Package for the Social Sciences, SPSS, Chicago). The normality of the data was examined by Kolmogorov-Smirnov test. If the data met the parametric conditions, independent samples were analyzed by t-test for two independent groups and ANOVA test for more than two groups. Tukey test was used for those who provided the homogeneity assumption and Tamhane T2 test was used for those who did not provide the homogeneity assumption to determine which group was different from the others. If any or all of the assumptions were not met, the Mann-Whitney U test for two independent groups and the Kruskal Wallis test for more than two independent groups were used. Chi-square test was used to evaluate the data obtained by counting. The error level was taken as 0.05. Continuous data were summarized as "Mean ± standard deviation (SD)" and "Median (interquartiles, IQR)".

## Results

In our single-center study, 714 patients who underwent bilateral total thyroidectomy with a diagnosis of PTC and received postoperative RAI treatment between 2012 and 2020 were included. Multifocality was detected in 142 (19.88%) of these patients. The mean age of PTC patients with multifocality was 50, and 108 of these patients were female (76.1%), and 34 were male (23.9%). When the number of patients showing multifocality by years is examined; multifocality was detected in 3 (3.29%) of 91 patients in 2012, 6 (7.2%) of 83 patients in 2013, 9 (10.1%) of 89 patients in 2014, 9 (10.5%) of 85 patients in 2015, 29 of 76 patients (38.15%) in 2015, 19 of 60 patients (31.6%) in 2017, 20 of 60 patients (33.33%) in 2018, 29 of 89 patients (32.58%) in 2019 and 8 of 81 patients in 2020 (22.22%) (Table 1). There was no significant difference in patient

**Table 1:** Multifocality Rate in Papillary Thyroid Cancer Patients by Years

| Year | PTC | Multifocal PTC | % |
|---|---|---|---|
| 2012 | 91 | 3 | 3.29 |
| 2013 | 83 | 6 | 7.2 |
| 2014 | 89 | 9 | 10.1 |
| 2015 | 85 | 9 | 10.5 |
| 2016 | 76 | 29 | 38.15 |
| 2017 | 60 | 19 | 31.6 |
| 2018 | 60 | 20 | 33.33 |
| 2019 | 89 | 29 | 32.58 |
| 2020 | 81 | 18 | 22.22 |
| Total | 714 | 142 | 19.88 |

age (p=0.544) and gender distribution by years (p=0.876).

Of the patients diagnosed with multifocal PTC, the tumor was 2-focused in 74 (52.1%), 3-focused in 29 (20.4%), 4-focused in 22 (15.5%), and 5 or more focused in 17 (12%) patients (Table 2). There was no significant relationship between tumor foci numbers and gender (p=0.538). It was observed that 88 of the patients (62%) were over the age of 45, and 54 (38%) of them were under the age of 45. However, no significant relationship was found between the number of tumor foci and bilateral or unilateral locations of the tumors and age (p=0.781 and 0.785, respectively). There was no significant relationship between the tumor's location in one or two lobes and the age of the patient (p=0.833). There was no significant correlation between tumor foci number and soft tissue invasion, angiolymphatic invasion, and initial lymph node metastasis (p=0.174, p=0.953, p=0.645, respectively). A significant correlation was found between the number of tumor foci and tumor differentiation (p=0.024). It was found that as the number of tumor foci increased, differentiation decreased.

In 48 patients (33.8%), multifocality was in a single lobe, whereas in 94 patients (66.2%) the multifocal tumor was localized in both lobes and/or isthmus. In addition, the tumor was detected in the right and left lobe in 77 patients (54.2%), in the isolated right lobe of 30 patients (21.1%), and in the isolated left lobe of 18 patients (12.7%). However, no patient was found to have multifocality only in the isthmus (p = 0.001).

There was a significant correlation between tumor localization and the largest tumor size (p = 0.020). Median tumor size is 14 mm in the presence of tumors located only in the right lobe, while it is 12.5 mm in those located only in the left lobe. In patients where the tumor is located in both lobes, the median tumor size is 16 mm (Table 3). No difference was found in terms of the largest tumor size by years (p = 0.740) (Table 4).

It was observed that multifocality was more common in microcarcinomas. All of the multifocal tumors were microcarcinoma (less than 1 cm) in 31 patients (21.8%), both microcarcinomas and tumors larger than 1 cm were present in 88 patients (62%), while in 23 patients (16.2%) all tumors were larger than 1 cm (Table 2).

Ablation success was found to be 78.2% in patients. No significant correlation was found between tumor foci numbers and tumor size and ablation success (p=0.287 and p=0.161, respectively). In addition, there was no significant correlation between tumor location (localization in one lobe or two lobes) and ablation success (p=0.838).

## Discussion

Multifocality is frequently seen in PTC patients, which are the most common thyroid cancer. There are controversies in the literature regarding the prognostic effect of multifocality in differentiated thyroid cancers. Geron et al. reported evidence that multifocality in PTC is not an independent prognostic factor but rather a marker of the extensiveness of the disease (15). However, in a meta-analysis by Joseph et al., it was reported that multifocality is a significant risk factor in both disease recurrence and disease progression (9). For this reason, more aggressive approaches are recommended in the management of patients with multifocality. According to the American Thyroid Association guideline, multifocality in tumors below 1 cm does not constitute an indication for RAI treatment (16). However, Malandrino et al.

**Table 2.** Multifokal Tumor Focus Number in PTC Patients and tumor Dimensions

| Tumor Focus Number | Number of Patients | % |
|---|---|---|
| 2 Focus | 74 | 52.1 |
| 3 Focus | 29 | 20.4 |
| 4 Focus | 22 | 15.5 |
| 5 and above | 17 | 12 |
| Dimensions | Number of Patients | % |
| All Foci are Microcarcinoma | 31 | 21.8 |
| Microcarcinoma and above 1cm | 88 | 61.9 |
| All of tumor above 1cm | 23 | 16.2 |
| Total Patients | 142 | 100 |

**Table 3.** Multifocal PTC Localization and Median Tumor Size

| Localization | Number of patients | % | Median Tumor Size | p |
|---|---|---|---|---|
| Right Lobe | 11 | 21.1 | 14 | |
| Left Lobe | 2 | 12.7 | 12,5 | |
| Isthmus | 1 | 0 | 0 | |
| Right and Left Lobe | 1 | 54.2 | 16 | p=0,020 |
| Isthmus, Right and Left Lobe | 2 | 8.5 | 19 | |
| Right Lobe and Isthmus | 1 | 1.4 | 8.5 | |
| Left Lobe and Isthmus | 1 | 2.1 | 35 | |
| Total | 19 | 100 | | |

Tumor localization and median tumor size are given in multifocal PTC patients. It was found that the location of the tumor significantly affected the median tumor size ($p < 0.05$)

reported that even if the tumor is microcarcinoma, the risk of recurrence is high in the case of multifocality (17). Therefore, some centers apply RAI ablation therapy in patients with multifocal thyroid cancer despite having microcarcinoma. This practice is usually done in our center. Thyroid tissue has an affinity for iodine element and this affinity plays a role in the mechanism of RAI ablation therapy (13). Since radioactive iodine reaches the tissue through blood, RAI ablation can be easily achieved in a tissue with sufficient blood circulation. In our study, no significant relationship was found between the number of tumor foci, tumor size, and localization of the tumor and the success of RAI ablation. These findings were consistent with the literature.

Our center, it was observed that there was no significant increase in the number of patients who received RAI treatment for PTC. However, when the histopathological data were examined, it was seen that the rate of multifocality increased significantly (Table 1). When patients with multifocal tumors were examined, the tumor was in 2 foci in 54% of the patients. However, it was seen that as the number of tumor foci increased, differentiation decreased. Therefore, it is thought that multifocal tumors may be decisive for treatment regardless of their size.

Tumor size has been the subject of many studies in recent years. In particular, microcarcinomas (<1 cm tumor) have been shown to be associated with multifocality (18). In our study, foci in multifocal PTC patients generally appear as microcarcinomas. Thyroid microcarcinomas are frequently detected in autopsy series and other surgical operation materials (1-36% and 24%, respectively). Bentrem et al. reported the rate of incidentally found malignant nodules as 12% in patients who underwent surgery for primary hyperparathyroidism (19). Evranos et al. reported that 36% of patients diagnosed with thyroid cancer were detected incidentally (20).

When the regions with multifocal PTCs are examined, it can be observed bilaterally in the thyroid gland, or it can be located in a multi-foci in a single lobe. In our study, in accordance with the literature, the tumor was located in the right and left lobes in 54.2% of the patients (21). However, interestingly, isolated multifocal PTC in the isthmus was not detected in any of our patients.

**Table 4.** Largest Tumor Size by Years

| Year | Mean | Median | Minimum | Maximum | Number of Patients |
|---|---|---|---|---|---|
| 2012 | 16.33 | 19 | 2 | 28 | 3 |
| 2013 | 22.33 | 20 | 7 | 45 | 6 |
| 2014 | 25.56 | 11 | 2 | 80 | 9 |
| 2015 | 19.56 | 17 | 6 | 40 | 9 |
| 2016 | 18.66 | 13 | 6 | 60 | 29 |
| 2017 | 14.05 | 12 | 6 | 35 | 19 |
| 2018 | 21.5 | 16,5 | 2 | 65 | 20 |
| 2019 | 20.72 | 15 | 4 | 62 | 29 |
| 2020 | 22.72 | 17 | 7 | 60 | 18 |

Many studies have shown a low probability of thyroid cancer in the isthmus region of the thyroid gland (22). However, no isolated multifocal PTC patient localized in the isthmus was found in the literature. We think that the reason for this may be the smaller size of the isthmus or the location of the vascular structures feeding the isthmus.

In our study, a significant relationship was found between the presence of PTC in both lobes and tumor size. We found that the median tumor size was lower with the tumor being in a single lobe or accompanied by the isthmus in any lobe. It was thought that the tumor tissue having the opportunity to benefit more from the vascular structures may cause this situation.

There are different data in the literature regarding the relationship of multifocality with age. In the study of Polat et al., no significant difference was found between the mean ages of patients in tumors with unilateral and bilateral locations (21). Consistent with the literature, in our study, no significant relationship was found between the tumor's location in one or two lobes and the age of the patient (p=0.833).

In our clinic, we have observed that the rate of multifocal PTC has increased in recent years. This significant increase may be the result of developments in diagnosis and treatment, as well as the morphological changes that occur over time in thyroid cancer. We think that our study may lead to future studies on this subject.

**Author Contributions:** MG: Conceptualization, Methodology, Writing - original draft, Writing - review & editing

MAG: Acquisition, Software, Writing - review & editing

SAE: Validation, Visualization, Writing - review & editing

ZH: Acquisition, Investigation, Methodology, Writing - review & editing

**Data Availability Statement**: Data supporting the findings of this study are available from the corresponding author.

**Conflict of Interest:** Muhammed Gömeç, Mustafa Asım Gedikli, Seyit Ahmet Türk, and Zekiye Hasbek have no confict of interest to disclose.

**Ethical Approval:** The present study protocol was reviewed and approved by the Institutional Review Board of Cumhuriyet University College of Medicine (Approval No. 2021-03/30).

**Informed Consent:** It is a retrospective study.

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