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Original study

Clinicopathological features of patients with coexistence of secondary hyperparathyroidism and incidental papillary thyroid carcinoma

Sekonder hiperparatiroidizm ve tesadüfen papiller tiroid karsinomu birlikteliği olan hastaların klinikopatolojik özellikleri

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ABSTRACT

The clinicopathological features of Secondary hyperparathyroidism (SHPT)-associated papillary thyroid carcinoma (PTC) are unclear and further investigation is required. In this study, it was aimed to evaluate the rate of PTC and tumor characteristics in the results of thyroidectomy performed for non-tumor reasons in patients with SHPT.

The data of 54 patients who underwent thyroidectomy with parathyroidectomy due to SHPT were analyzed. The patients were divided into two groups; patients with thyroid malignancy (group M) and patients without (group B).

PTC was detected in 12 (22.2%) of 54 patients who underwent parathyroidectomy and thyroidectomy for SHPT. There was no difference between the groups in terms of gender (p=0.95), age (p=0.75), duration of hemodialysis (p=0.30). Preoperative mean parathormone level was higher in patients with malignancy (p=0.02). The thyroid nodule sizes of the patients in Group M were statistically significantly larger (17.8 ± 9.1 mm vs 13.09 ± 4.73 mm, p=0.02). Recurrence of PTC developed in the 19th month of the follow-up in one of our patients. The mean follow-up period of all patients was 22 ± 20.72 months.

In order not to overlook the association of PTC in patients with SHPT, surgeons should perform adequate preoperative examinations and be more careful during surgery.

Keywords: Secondary hyperparathyroidism; papillary thyroid carcinoma; end stage renal disease

ÖZET

Sekonder hiperparatiroidizm (SHPT) ile ilişkili papiller tiroid karsinomunun (PTC) klinikopatolojik özellikleri belirsizdir ve daha fazla araştırma yapılması gerekmektedir. Bu çalışmada SHPT'li hastalarda tümör dışı nedenlerle yapılan tiroidektomi sonuçlarında PTK oranının ve tümör özelliklerinin değerlendirilmesi amaçlandı.

SHPT nedeniyle paratiroidektomi ile birlikte tiroidektomi uygulanan 54 hastanın verileri analiz edildi. Hastalar iki gruba ayrıldı; tiroid malignitesi olan hastalar (grup M) ve olmayan hastalar (grup B).

SHPT nedeniyle paratiroidektomi ve tiroidektomi yapılan 54 hastanın 12'sinde (%22,2) PTK saptandı. Gruplar arasında cinsiyet (p=0,95), yaş (p=0,75), hemodiyaliz süresi (p=0,30) açısından fark yoktu. Maligniteli hastalarda ameliyat öncesi ortalama parathormon düzeyi daha yüksekti (p=0,02). Grup M'deki hastaların tiroid nodül boyutları istatistiksel olarak anlamlı derecede daha büyüktü (17,8 ± 9,1 mm vs 13,09 ± 4,73 mm, p=0,02). Bir hastamızda takibin 19. ayında PTC nüksü gelişti. Tüm hastaların ortalama takip süresi 22±20,72 ay idi.

SHPT'li hastalarda PTK birlikteliğini gözden kaçırmamak için cerrahların ameliyat öncesi yeterli muayeneleri yapmaları ve ameliyat sırasında daha dikkatli olmaları gerekmektedir.

Anahtar kelimeler: Sekonder hiperparatiroidi; papiller tiroid karsinomu; son dönem böbrek hastalığı

INTRODUCTION

Secondary hyperparathyroidism (SHPT), a common complication of end-stage renal disease (ESRD), can develop in almost all patients with chronic kidney disease. It is responsible for bone pain, itching, mineral bone disorders, ectopic calcification, anemia, myopathy, malnutrition, neuropathy, and cardiovascular problems with a high risk of death (1). Some patients with early stage SHPT may have a successful response to medical therapy; however, surgical intervention is required in advanced stages of the disease because drug therapy is ineffective or the parathyroid hormone (PTH) level rises above a certain range (2). Papillary thyroid carcinoma (PTC), the most common thyroid carcinoma (TC), is a slowly progressive tumor with a low mortality rate (3). The high incidence of TC in patients with ESRD has led to increased interest in investigating the effect of SHPT on TC in terms of tumor formation and biological behavior (4). The relationship between primary hyperparathyroidism (PHPT) and TC was first described about 75 years ago (5). Recent studies have evaluated the necessity and extent of thyroid examination before parathyroid surgery. It has been defined that patients with SHPT are also associated with thyroid nodular disease and cancer (6). However, the clinicopathological features of SHPT-associated PTC are unclear and further investigation is required. In this study, it was aimed to evaluate the rate of PTC and tumor characteristics in the results of thyroidectomy performed for non-tumor reasons in patients with SHPT.

MATERIAL and METHOD

The study protocol was approved by the Ethics Committee of the University. All procedures were performed with the ethical standards of the institutional and national research committee and the 1964 Declaration of Helsinki. Informed consent was obtained from all participants included in the study.

For the study, the data of 126 patients who underwent parathyroidectomy due to SHPT in our department between April 2010 and January 2022 were retrospectively analyzed from the prospective parathyroid surgery database followed since April 2010. Patients who underwent thyroidectomy along with parathyroidectomy were selected (54 patients). According to the thyroidectomy pathology results, the patients were divided into two groups; patients with thyroid malignancy (group M) and patients without (group B).

Indications for parathyroidectomy were based on the 2009 KDIGO guidelines on CKD and mineral-bone disorders (7). All patients had previously been treated with calcimimetic agents for at least one year and were referred for initial parathyroidectomy due to medically refractory SHPT. Thus, patients who, despite maximized medical treatment, failed to maintain appropriate levels of serum calcium (8.4–10.2 mg/dL), phosphate (2.5–4.6 mg/dL) and PTH between two to nine times the normal upper limit (130– 600 pg/mL), were referred for surgery. Total parathyroidectomy was planned for all patients.

Patients with coexistence of SHPT and thyroid nodules were evaluated according to the current American Thyroid Association (ATA) guidelines (8–10). Simultaneous thyroidectomy was required due to solitary / multinodular goiter or failure to identify the fourth parathyroid gland during bilateral neck exploration. None of the patients had histopathological and radiopathological findings of thyroid malignancy before parathyroidectomy.

The Access Intact PTH assay (Access Immunoassay Systems Intact PTH A16972, Beckman Coulter, Inc., Fullerton, CA) was used for quantitative determination of intact parathyroid hormone levels in human serum and plasma. The reference interval of this immunoassay kit is 12–88 pg/mL.

Statistical analyzes were performed using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). Descriptive statistics for continuous variables are expressed as mean ± standard deviation, and non-normally distributed variables are expressed as median (min–max). Bivariate analysis was conducted with independent sample t-test, to compare means. Categorical variables are expressed as number and percentage, and Fisher's Chi-square test was used to assess the differences between groups with regard to categorical variables. Differences were considered statistically significant at $p < 0.05$.

RESULTS

PTC was detected in 12 (21.4%) of 56 patients who underwent parathyroidectomy and thyroidectomy for SHPT. Group B and group M

were similar in terms of gender (female 40.9%, 40% and p=0.95, respectively). The mean age of group B was 51.4 ± 11.9 years, and group M was 50.1 ± 11.8 years (p=0.75). The mean duration of hemodialysis was 108.8 ± 52.2 months in Group B and 90 ± 51.3 months in Group M (p=0.3). Preoperative mean parathormone level was higher in Group M (2147 ± 1132 vs 1375 ± 889, p=0.02). In the neck ultrasonography performed in the preoperative period, nodules were detected in 47.7% of the patients in Group B and in 80% of the patients in Group M. Although thyroid nodules were seen more frequently in patients with malignancy, no statistically significant difference was observed (p=0.13). Eighteen (40.9%) patients in group B and eight (75%) in group M were multinodular. Although multinodularity was proportionally higher in patients with PTC, no statistically significant correlation was found between multinodularity and PTC (p=0.18). The thyroid nodule sizes of the patients in Group M were statistically significantly larger (17.8 ± 9.1 mm vs 13.09 ± 4.73 mm, p=0.02). No malignancy was detected in preoperative thyroid fine aspiration biopsy in any patient in both group B and group M. Bilateral total thyroidectomy was performed in 12 (27.2%) patients in Group B and 5 (41.6%) patients in Group M (p=0.68). Three patients (11mm, 12mm, and 15mm) in Group M with tumors larger than 1 cm were also among those who underwent bilateral total thyroidectomy. We had a patient with a 4 mm PTC in one focus after unilateral thyroidectomy. Considering the patient's wishes, it was decided not to perform a complementary thyroidectomy. Complementary thyroidectomy was performed at the 19th month of follow-up due to the development of recurrent PTC. The mean follow-up period of all patients was 22 ± 20.72 months. The tumor was multifocal in five patients in Group M, and the mean tumor diameter of all patients was 5.6 ± 5.9 mm. The subgroups of patients with PTC and the histopathological results of patients with benign pathology after thyroidectomy are summarized in Figure 1 and 2. Postoperative hemorrhage and recurrent laryngeal nerve damage were not observed in any patient in either group.

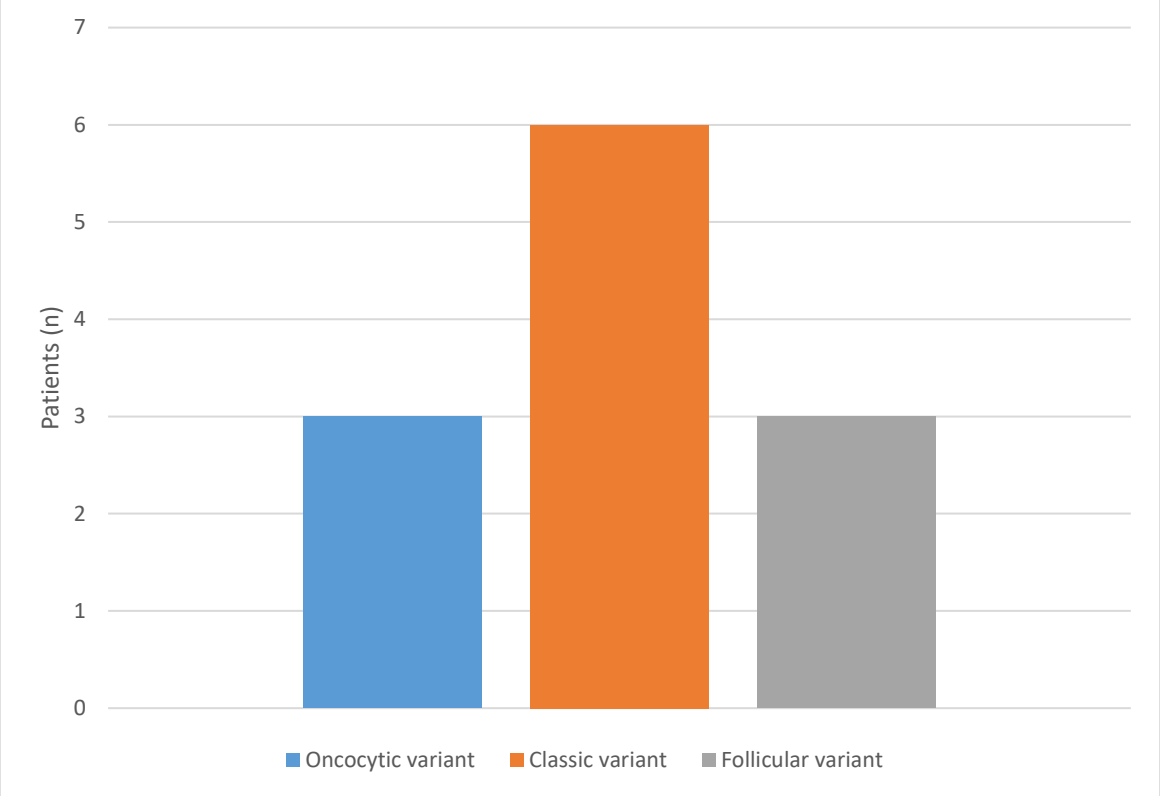

Figure 1: Distribution of patients with papillary thyroid carcinoma according to histopathological subgroups.

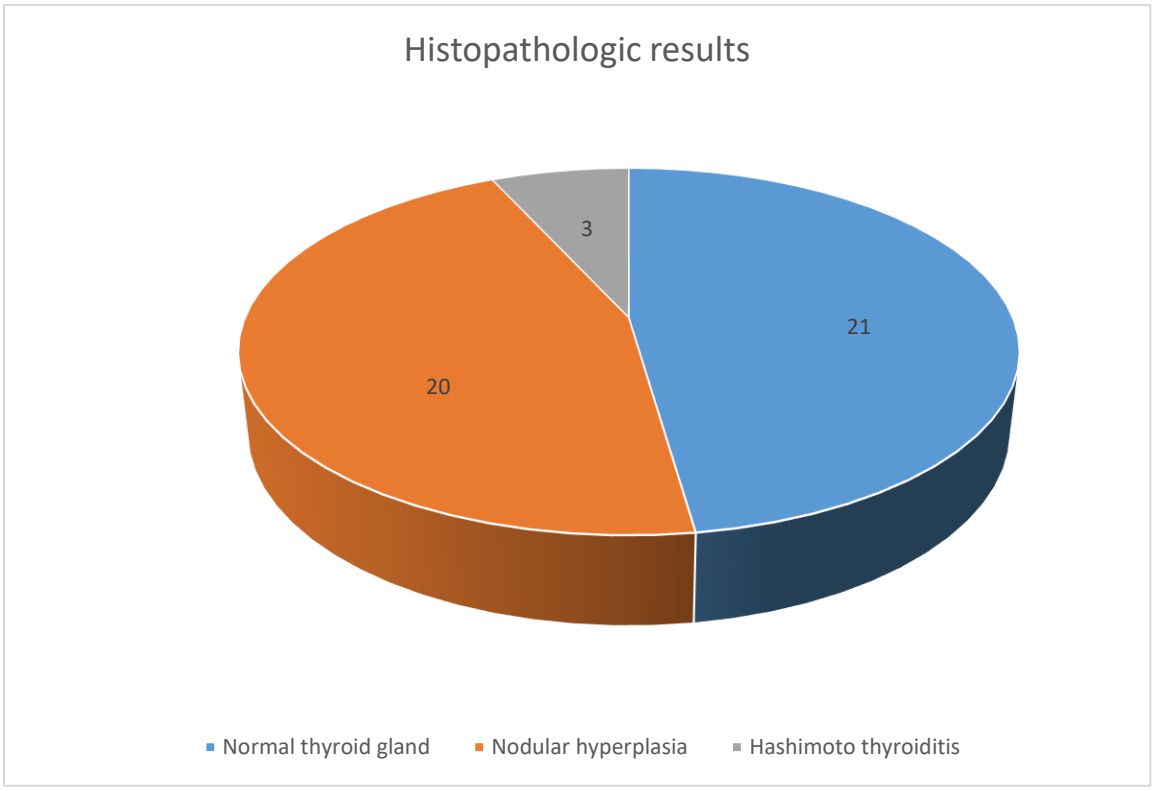

Figure 2: Histopathological results of patients with benign pathology.

DISCUSSION

In this study, the data of 126 patients who underwent parathyroidectomy for SHPT were reviewed retrospectively. Demographic, laboratory and radiological data of patients with and without PTC among 56 patients who underwent simultaneous thyroidectomy were compared. Histopathological results of thyroidectomy specimens were analyzed.

There are many studies in the literature that ESRD increases many malignancies, including PTC. Although all these studies suggest that ESRD is accompanied by an increased risk of malignancy, including PTC, they have not systematically evaluated patients with SHPT who have undergone both parathyroidectomy and thyroidectomy.

According to previous studies, metabolic disorders of calcium, phosphorus and vitamin D caused by SHPT, immunological deficiency accompanied by ESRD and advanced age; It has been suggested that it plays a role in thyroid dysfunction and PTC formation-development (11,12). Lin et al revealed that SHPT increased the risk of PTC approximately 10.1 times in patients with ESRD (13). On the other hand, in a study examining 339 patients with SHPT due to ESRD, the incidence of PTC was shown to be 2.4% (14). PTC detection rates ranging from 5% to 11% are known in autopsy series, so the relationship between PTC and SHPT is questionable. Whether ESRD and/or SHPT can induce a higher incidence rate of PTC is still debated. Our study showed that the incidence of incidentally detected PTC in the group of patients with SHPT who required surgery was higher than the incidence in the general population in Turkey (16.2/100.000) (21.4% in those who underwent thyroidectomy, 9.5% in the whole patient group) (15). Therefore, we believe that SHPT is a risk factor for PTC. Although it is known that ESRD increases TC, we could not detect a relationship between the duration of ESRD and the development of TC. Burmeister et al, in their study including 824 patients in which they examined the relationship between primary-secondary-tertiary hyperparathyroidism and TC, could not find a significant relationship between the duration of ESRD and TC (16).

The most common type of thyroid surgery performed simultaneously in HPT is total/subtotal thyroidectomy or unilateral lobesthmectomy (17). The most common histological findings described in the literature are nodular goiter (8.4-47% of HPT cases), followed by thyroiditis (1.4-17.6%) and solitary thyroid adenoma (3.8-6.4%) (18). Graves' disease is a rare histopathological finding (1.8%) (19). Our findings are similar to these previous results.

Gender is known to be associated with PTC. It is 2.9 times more common in women than men. Similar to studies (16) stating that female gender does not increase the risk of PTC among patients with HPT, there was no gender difference between SHPT and SHPT+PTC groups in our study group.

Preoperative PTH levels were found to be statistically higher in the SHPT+PTC patient group

in our study. This result may raise the question that elevated parathormone levels may predispose to malignancy, but this issue is controversial in the literature (16). Preda C et al, in their study examining the relationship of SHPT and PHPT to PTC, found the incidence of PTC to be similar, although PHT levels were higher in the SHPT group in the preoperative period (25.3% in PHPT and 29% in SHPT, p = 0.694) (18) .

In another study examining the relationship between SHPT and PTC (18), PTC was found in 25.7% of patients who underwent parathyroidectomy and simultaneous thyroidectomy. All of the tumors are microcarcinomas and in 88.8% of the patients, the tumor is unifocal. In our study, the multifocality rate was 41.6% and 75% of the tumors were microcarcinomas. In patients with SHPT, PTC is frequently seen in micropapillary morphology, in this sense, the results in our study are similar to the literature. However, multifocality was more common in our patient group. The tumor nature of PTC is also prone to multifocal spread, but the different results in the spread pattern of PTCs in patients with SHPT are open to study.

It has been suggested that papillary thyroid carcinomas in the PTC + SHPT group are often occult PTC and present a slower tumor phenotype associated with minimal tissue trauma and maximum thyroid function retention (6). The fact that 75% of the patients in our study had microcarcinoma pathology also supports this data. It has been previously proven that PTC has a good prognosis with very low mortality (20). A previous study has shown that the recurrence rate of PTC is approximately 1-5% (21). In our study, recurrence was observed in one patient in the PTC + SHPT group who underwent unilateral thyrodectomy. Although it was stated in previous studies that SHPT is not a risk factor for PTC recurrence, recurrence was seen at a higher rate (8.3% vs 1-5%) in our study compared to literature data. We think that it may be related to the small size of our patient group. Studies conducted in larger patient groups may be instructive.

This study has several limitations. The sample size of the study was limited and the follow-up period was short. Therefore, more prospective randomized controlled trials with larger sample sizes and longer follow-up times are needed to further validate the study results.

Conclusion

In conclusion, the prevalence of PTC is high in patients with SHPT; therefore, clinicians should be aware that PTC may coexist during surgery. Compared with PTC in the general population, most papillary thyroid carcinomas with SHPT are micropapillary thyroid carcinomas, and tumor pathological features do not differ significantly in terms of prognostic staging. In order not to overlook the association of PTC in patients with SHPT, surgeons should keep in mind the association of PTC during preoperative examinations.

Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Ethics committee approval of our center was obtained with the decision numbered 2018/02/05.

REFERENCES

1. Tentori F, Wang M, Bieber BA, Karaboyas A, Li Y, Jacobson SH, et al. Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS study. Clin J Am Soc Nephrol. 2015;10(1):98–109.
2. Garabed E, Norbert L, Bertram LK. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). Kidney International Supplement. 2017;7(1):1–59.
3. Roman BR, Morris LG, Davies L. The thyroid cancer epidemic, 2017 perspective. Curr Opin Endocrinol Diabetes Obes. 2017;24(5):332.
4. Kantor AF, Hoover RN, Kinlen LJ, McMullan MR, Fraumeni Jr JF. Cancer in patients receiving long-term dialysis treatment. Am J Epidemiol. 1987;126(3):370–376.
5. Kissin M, Bakst H. Co-existing myxedema and hyperparathyroidism: case report. J Clin Endocrinol. 1947;7(2):152–158.
6. Ma J, Mao Z, Yao Y, Lu Y, Wang H, Yang Y, et al. Coexistence of papillary thyroid carcinoma in secondary hyperparathyroidism. BMC surg. 2021;21(1):1–6.

7. Group KDIGO (KDIGO) C-MW. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009;(113):S1–130.
8. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, 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. 2016;26(1):1–133.
9. Cooper DS. American Thyroid Association (ATA) guidelines taskforce on thyroid nodules and differentiated thyroid cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19:1167–1214.
10. Haugen BR. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: what is new and what has changed? Cancer. 2017;123(3):372–381.
11. Kaptein EM. Thyroid hormone metabolism and thyroid diseases in chronic renal failure. Endocr Rev. 1996;17(1):45–63.
12. Vamvakas S, Bahner U, Heidland A. Cancer in end-stage renal disease: potential factors involved. Am J Nephrol. 1998;18(2):89–95.
13. Lin S-Y, Lin W-M, Lin C-L, Yang T-Y, Sung F-C, Wang Y-H, et al. The relationship between secondary hyperparathyroidism and thyroid cancer in end stage renal disease: a population based cohort study. Eur J Intern Med. 2014;25(3):276–280.
14. Seehofer D, Rayes N, Klupp J, Nüssler NC, Ulrich F, Graef K-J, et al. Prevalence of thyroid nodules and carcinomas in patients operated on for renal hyperparathyroidism: experience with 339 consecutive patients and review of the literature. World J Surg. 2005;29(9):1180–1184.
15. 2017 Yılı Türkiye Kanser İstatistikleri [Internet]. Available from: https://hsgm.saglik.gov.tr/tr/kanser-istatistikleri
16. Burmeister LA, Sandberg M, Carty SE, Watson CG. Thyroid carcinoma found at parathyroidectomy: association with primary, secondary, and tertiary hyperparathyroidism. Cancer. 1997;79(8):1611–1616.
17. Kutlutürk K, Otan E, Yağcı MA, Usta S, Aydın C, Ünal B. Thyroid pathologies accompanying primary hyperparathyroidism: a high rate of papillary thyroid microcarcinoma. Turk J Surg. 2014;30(3):125.
18. Preda C, Branisteanu D, Armasu I, Danila R, Velicescu C, Ciobanu D, et al. Coexistent papillary thyroid carcinoma diagnosed in surgically treated patients for primary versus secondary hyperparathyroidism: same incidence, different characteristics. BMC Surg. 2019;19(1):1–10.
19. Masatsugu T, Yamashita H, Noguchi S, Nishii R, Watanabe S, Uchino S, et al. Significant clinical differences in primary hyperparathyroidism between patients with and those without concomitant thyroid disease. Surg Today. 2005;35(5):351–356.
20. Ieni A, Barresi V, Cardia R, Licata L, Di Bari F, Benvenga S, et al. The micropapillary/hobnail variant of papillary thyroid carcinoma: a review of series described in the literature compared to a series from one southern Italy pathology institution. Rev Endocr Metab Disord. 2016;17(4):521–527.
21. Leboulleux S, Tuttle RM, Pacini F, Schlumberger M. Papillary thyroid microcarcinoma: time to shift from surgery to active surveillance? Lancet Diabetes Endocrinol. 2016;4(11):933–942.