



# Simultaneous Occurrence of Different Follicular Neoplasms within the Same Thyroid Gland

## Aynı Tiroid Bezinde Farklı Foliküler Hücre Kökenli Neoplazilerin Birlikteliği

Şefika Burçak Polat, Dilek Arpacı\*, Aylin Yazgan\*\*, Hüsnüye Başer, Mehmet Kılıç\*\*\*, Reyhan Ersoy, Bekir Çakır

Yıldırım Beyazıt University Atatürk Training and Research Hospital, Clinic of Endocrinology and Metabolism, Ankara, Turkey

\*Karaelmas University Faculty of Medicine, Department Endocrinology and Metabolism Department, Zonguldak, Turkey

\*\*Yıldırım Beyazıt University Atatürk Training and Research Hospital, Clinic of Pathology, Ankara, Turkey

\*\*\*Yıldırım Beyazıt University Atatürk Training and Research Hospital, Clinic of General Surgery, Ankara, Turkey

### Abstract

**Purpose:** Neoplasms of the thyroid gland are classified according to the cells they originate from and commonly develop from cells of follicular origin. The most common differentiated thyroid cancers (DTC) are papillary and follicular carcinomas. Coexistence of two different histological types of primary follicular thyroid neoplasm is a rare condition. There are previous reports of concomitant medullary and papillary thyroid cancers. However, there is scarce data about the simultaneous occurrence of the two different histological types of primary follicular thyroid tumors and this is the first study on that subject.

**Material and Method:** From January 2007 to September 2014, our institutional database was reviewed for patients who underwent thyroid surgery for various indications. Medical records and cytopathology reports of those patients were examined retrospectively. Simultaneous neoplasms of follicular origin were noted.

**Results:** A total of 3.700 patients were operated. Histopathological examination revealed a benign pattern in 2.686 (73%) patients and a malignant pattern in 1.014 (27%) patients. Among the patients with the diagnosis of DTC, only 20 (1.9%) had a concomitant neoplasm within the same thyroid gland.

**Discussion:** Such simultaneous tumors may be a part of a familial tumor syndrome or an unidentified novel gene mutation playing role in the pathogenesis of more than one type of tumor. Based on the current evidence, the synchronous occurrence of those neoplasms in a given patient is likely coincidental in the literature. Further studies on larger patient population with standardized genetic characterization are needed.

**Keywords:** Simultaneous follicular neoplasms, mixed tumors, adenomas, carcinoma

### Öz

**Amaç:** Tiroid bezinin neoplazileri köken aldıkları hücreye göre sınıflandırılır ve çoğunlukla foliküler hücrelerden köken alır. En sık görülen iki diferansiye tiroid kanseri (DTK) tipi papiller ve foliküler karsinomdur. Daha önce literatürde aynı hastada medüller ve papiller karsinom birlikteliği rapor edilmiştir. Ancak iki farklı histolojik tipte foliküler tümörün simültane birlikteliği ile ilgili bir yayın yoktur.

**Gereç ve Yöntem:** Hastanemiz tiroid veri tabanı 2007-2014 yılları arasında çeşitli endikasyonlarla yapılmış tiroidektomi operasyonlarına ait patoloji raporları açısından tarandı. Aynı tiroid bezinde farklı iki foliküler neoplazisi olan hastalar kaydedildi.

**Bulgular:** Veri tabanında toplam 3.700 hastanın tiroidektomiye ait histopatoloji sonucu mevcut idi. Bu hastaların 2.686'sında (%73) patoloji benign, 1.014'ünde (%27) patoloji malign idi. DTK tanısı konulan hastaların sadece 20'sinde (%1,9) eşlik eden ikinci bir foliküler hücre kökenli tümör mevcut idi.

**Tartışma:** Aynı tiroid bezinde farklı tipte neoplazilerin birlikteliği ailesel tümör sendromları veya birden fazla tümörün patogeneğinde rol oynayan gen mutasyonlarının varlığı ile ilişkili olabilir. Şu andaki bilimsel kanıtlara dayanarak senkron tümörlerin patofizyolojisini açıklamak mümkün olmadığı için şimdilik rastlantısal bir durum olarak kabul edilmektedir. Daha büyük hasta popülasyonları ile standardize genetik karakterizasyonun yapıldığı yeni çalışmalara ihtiyaç vardır.

**Anahtar kelimeler:** Simültane foliküler neoplaziler, kompozit tümörler, adenom, karsinom

## Introduction

Thyroid follicular cells renew themselves continuously, responding to various stimuli, such as thyrotropin, growth factors, cytokines, and iodine. Nodules develop when those growth signals increase and promote hyperplasia or when a new genetic mutation is acquired leading to autonomous growth (1). The main concern of the clinician while evaluating a thyroid nodule is to determine if the nodule is benign or malignant. The most useful diagnostic technique is fine needle aspiration biopsy in that regard.

Most of the thyroid nodules are benign while only 9-13% of them are malignant (2). Thyroid cancer is the most common endocrine malignancy and is one of the fastest growing cancers diagnosed in the Western world. The estimated incidence of thyroid cancer was more than 56.000 cases in 2012 in North America (3).

Among differentiated thyroid cancers, papillary carcinoma can be diagnosed with fine needle aspiration biopsy (FNAB). However, FNAB has limited usefulness in the diagnosis of follicular and Hurthle cell tumors since adenoma/carcinoma discrimination require demonstration of capsule invasion which is detected by histological examination (4).

Papillary thyroid carcinoma (PTC) is the most common histological type of differentiated thyroid carcinomas and it constitutes of 88% of all thyroid cancers. Follicular carcinoma (FC) and Hurthle cell carcinoma (HC) arise from the follicular cells of the thyroid and account for approximately 10% and 4% of thyroid malignancies, respectively (5,6). Papillary thyroid cancer has an excellent prognosis with a high cure rate and 10-year survival rate. FC is generally considered more aggressive with poorer prognosis compared with PTC and more likely to present with distant metastases on its initial diagnosis (7).

The simultaneous occurrence different neoplasms of follicular origin within the same thyroid gland is rare and that kind of presentation was named as mixed, composite or hybrid tumors previously.

There have been previous reports of simultaneous medullary and papillary thyroid cancers (8,9). However, there is scarce data about the coexistence of two different histological types of primary follicular thyroid tumors and this is the first study on that subject.

## Materials and Methods

This retrospective study was approved by The Institutional Ethics Board of Yıldırım Beyazıt University Atatürk Training and Research Hospital. Written informed consent was obtained from all patients before ultrasonographic-FNA or surgery prior to procedures. Our institutional database was reviewed for patients who underwent thyroid surgery for various indications (suspicious cytology, Graves' disease, toxic multinodular goiter, toxic adenoma, compression symptoms, etc.) between January 2007 and September 2014. Medical records and cytopathologic reports of those patients were examined retrospectively. Simultaneous neoplasms of follicular origin were noted.

### Statistical Analysis

Statistical analyses were performed with SPSS 15.0 (SPSS Inc., IL., USA) statistical soft-ware. Arithmetic mean  $\pm$  standard deviation

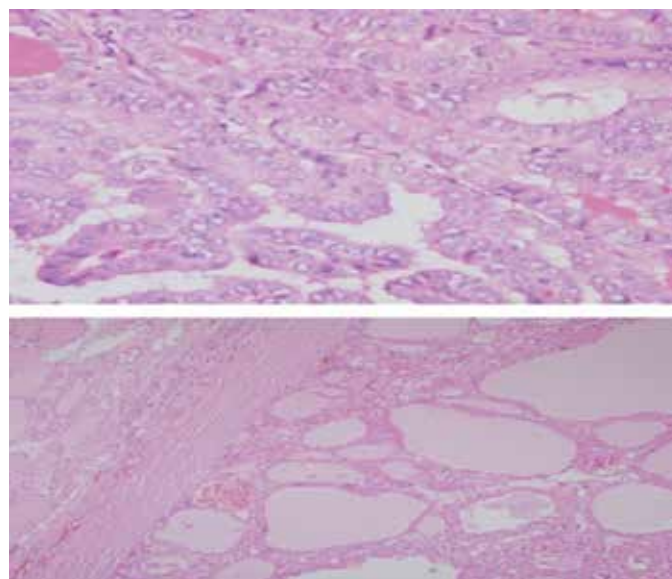
was used for descriptive statistics of the continuous data. Frequency tables were made for qualitative data.

## Results

A total of 3.700 patients were operated. Histopathological examination result was benign in 2.686 (73%) patients while it was malignant in 1.014 (27%) patients. Among the patients with the diagnosis of differentiated thyroid carcinoma only 20 (1.9%) had an accompanying neoplasm within the same thyroid gland. The mean age of the patients was  $48.8 \pm 13.2$  years. Eighteen of 20 patients were female and two were male. The mean TSH level was  $0.98 \pm 0.79$  uIU/mL. All the 20 patients had PTC plus a secondary neoplasm. PTC was classical variant in 17 while it was follicular variant in three patients. The mean size of the papillary tumor was  $10.6 \pm 10.46$  mm. PTC had thyroid capsule invasion in seven patients (35%) while the capsule was intact in 13 (65%). In 17 (85%) patients, there was no vascular invasion whereas in three patients (15%), PTC with vascular invasion was detected. Second neoplasm was FC in ten patients, HC in two patients, Hurthle cell adenoma in five patients and follicular adenoma (FA) in three patients. The mean size of the second neoplasms was  $20.4 \pm 15.4$  mm. Demographic features, laboratory data and pathology results are summarized in Table 1. Thyroid capsule invasion was present in all patients with HC and in nine of ten patients with FC as the second neoplasm. Vascular invasion was positive in 1 of 2 Hurthle cell carcinomas and six of ten FCs. Lymph node metastasis was detected in three of 20 patients. During the follow-up period (maximum seven years; minimum six months) three patients had recurrence/metastasis (Figure 1, 2, 3, 4).

## Discussion

The pathogenesis of mixed tumors were previously explained with common stem cell theory, collision theory which suggests simultaneous multifocal origin from different cell clones, or

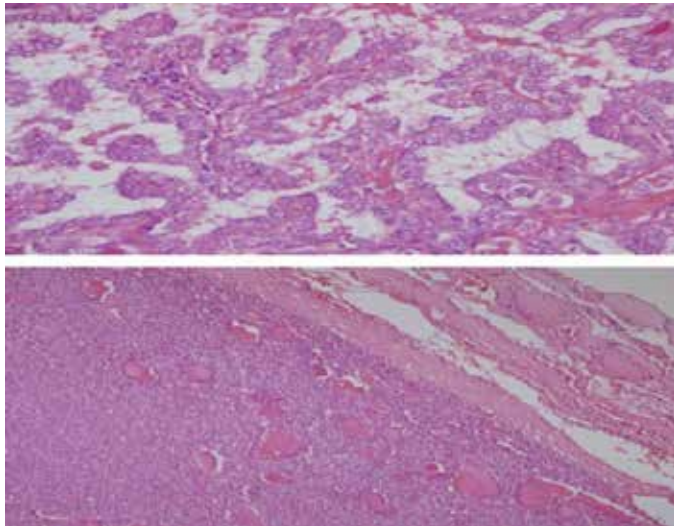


**Figure 1.** Papillary cancer and hurtle cell adenoma

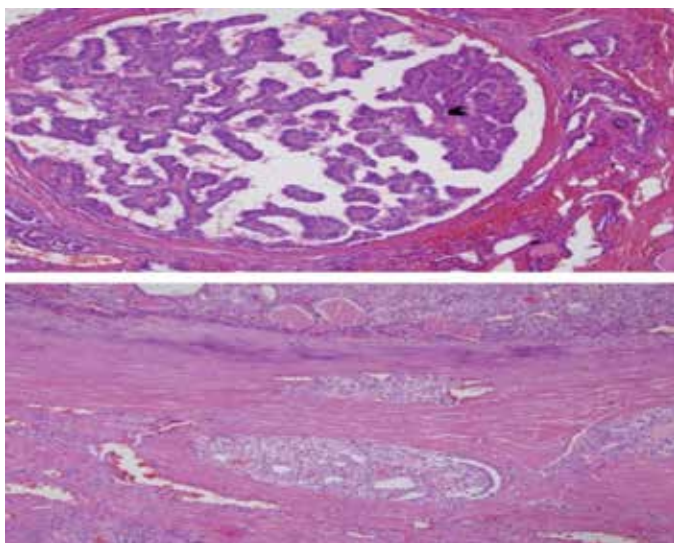
hostage theory which postulates that adenomatous areas are sequestered by another tumor type, though the exact mechanism is not enlightened (9,10).

Mixed tumors can occur as part of familial cancer syndromes such as Carney's complex, Werner's syndrome and Cowden's syndrome causing FA, PTC and FC (11,12). Age of the patients is younger in case of those familial or syndromic thyroid cancers compared to sporadic cases.

In our study, twenty patients diagnosed with papillary thyroid cancer had a second accompanying neoplasm within the same thyroid gland. Those tumors were FC, HC, FA and Hurthle cell adenoma. To our knowledge, simultaneous occurrence of two tumors of follicular origin is extremely rare. Most of the reports in the literature are medullary and follicular/papillary carcinoma compositions. In the present study, all tumors were sporadic and there were not the aforementioned associations of multiple endocrine neoplasm, familial history or bilaterally involved thyroid gland.



**Figure 2.** Papillary cancer and follicular adenoma



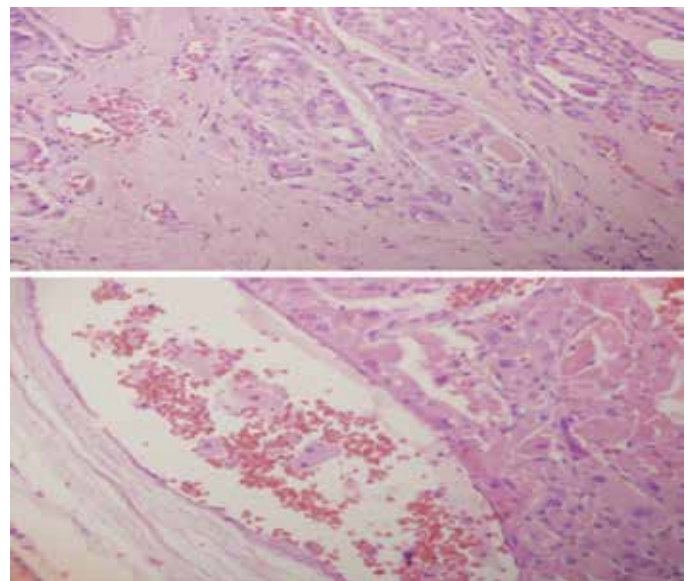
**Figure 3.** Papillary cancer and follicular carcinoma

Previously, Wu et al. (13) have reported a case of mixed medullary-FC and PTC of the same thyroid gland. They postulated that neoplastic transformation was either due to a tumorigenic stimulus or to the collision phenomenon. Ganguly et al. (14) reported a 64-year-old female patient with composite anaplastic and PTC on one thyroid lobe with a FC in the other lobe. The patient also had a separate and independent FA in the same lobe as the composite anaplastic and PTC. She underwent total thyroidectomy and bilateral neck lymph node dissection followed by chemotherapy and died two months after surgery. The authors postulated that anaplastic cancer could result from the dedifferentiation of a pre-existing differentiated carcinoma. Meinhard and Michailov (15) have reported a case of simultaneous occurrence of medullary and PTC in the same thyroid lobe. Cupisti et al. (16) have also reported a case of synchronous occurrence of a follicular, papillary and medullary thyroid carcinoma in a recurrent goiter. It was suggested that especially in iodine deficient areas, dedifferentiation patterns can be noted in PTC resembling FC.

For each type of thyroid carcinoma, several genes have been identified. Activating somatic mutations are involved in FC while rearranged during transfection/PTC, TRK and BRAF mutations are involved in PTC (17,18,19). In addition to those, p53 mutations are responsible for the post radiation PTC cases (20). However, there is no common gene mutation responsible for the pathogenesis of the different tumor types of the thyroid gland. Therefore, the simultaneous tumors in our patients will remain as coincidental until a novel genetic mutation is identified.

It has been proposed that the coincidence of these carcinomas arises from separate embryologic origins. The transformation of thyroid cells (thyroidal follicular cell and parafollicular cell) to neoplastic change due to uncertain episodes, such as tumorigenic stimulus may be an alternative explanation.

This is the first retrospective study on FC, PTC, HC or adenomas occurring simultaneously. Literature review of the past two decades does not reveal sufficient evidence to suggest genetically



**Figure 4.** Papillary cancer and hurthle cell carcinoma



Table 1. Clinical data of each patient with synchronous tumors

	Age	Sex	Preop diagnosis	PTC subtype	PTC size (mm)	Capsul invasion	Vascular invasion	LN met	Second neoplasm	Second tum size (mm)	Capsule invasion	Vascular invasion	LN met	RAI dose	Post RAI WBS extra thyroidal focus	Recurrence or metastasis during follow up
Case 1	58.0	F	MNG	Classic	3.0	Neg	Neg	Neg	FC	40.0	Pos	Pos	Neg	150.0	Neg	Neg
Case 2	43.0	M	MNG	Classic	5.0	Pos	Neg	Neg	FC	40.0	Pos	Pos	Pos	100.0	Neg	Neg
Case 3	37.0	F	MNG	Classic	3.0	Neg	Neg	Neg	FC (Oncocytic variant)	16.0	Pos	Pos	Neg	100.0	Neg	Neg
Case 4	22.0	F	MNG	Folic. V	32.0	Pos	Neg	Neg	FC	15.0	Pos	Neg	Neg	100.0	Pos	Neg
Case 5	42.0	F	MNG	Classic	20.0	Neg	Neg	Neg	FC	17.0	Pos	Pos	Neg	100.0	Neg	Neg
Case 6	37.0	F	MNG	Classic	7.0	Neg	Neg	Neg	FC	18.0	Neg	Neg	Neg	150.0	Neg	Neg
Case 7	57.0	F	MNG	Folic. V	10.0	Neg	Neg	Neg	TA	4.0	Neg	Neg	Neg	100.0	Neg	Neg
Case 8	35.0	F	MNG	Classical	12.0	Neg	Neg	Neg	FA	55.0	Neg	Neg	Neg	100.0	Neg	Neg
Case 9	60.0	F	MNG	Classical	3.0	Neg	Neg	Neg	HA	12.0	Neg	Neg	Neg	100.0	Neg	Neg
Case 10	39.0	F	MNG	Folic. V	7.0	Pos	Neg	Neg	FC	18.0	Pos	Neg	Neg	150.0	Neg	Neg
Case 11	52.0	F	MNG	Classical	12.0	Pos	Pos	Pos	FA	3.0	Neg	Neg	Neg	150.0	Neg	Neg
Case 12	62.0	F	MNG	Classical	2.0	Neg	Neg	Neg	HA	17.0	Neg	Neg	Neg	100.0	Neg	Neg
Case 13	63.0	F	MNG	Classical	3.0	Pos	Neg	Neg	HA	8.0	Neg	Neg	Neg	150.0	Neg	Neg
Case 14	80.0	F	MNG	Classical	24.0	Pos	Pos	Neg	HA	10.0	Neg	Neg	Neg	150.0	Neg	Neg
Case 15	60.0	M	MNG	Classical	2.0	Neg	Neg	Neg	HC	6.0	Pos	Neg	Neg	150.0	Neg	Neg
Case 16	49.0	F	MNG	Classical	16.0	Neg	Neg	Neg	HA	5.0	Neg	Neg	Neg	100.0	Neg	Neg
Case 17	52.0	F	MNG	Classical	3.0	Neg	Neg	Neg	HC	40.0	Pos	Pos	Neg	150.0	Neg	Pos
Case 18	48.0	F	MNG	Classical	2.0	Neg	Neg	Neg	FC	40.0	Pos	Pos	Neg	150.0	Neg	Pos
Case 19	36.0	M	MNG	Classical	8.0	Neg	Neg	Neg	FC	35.0	Pos	Pos	Neg	150.0	Neg	Neg
Case 20	44.0	F	MNG	Classical	38.0	Pos	Pos	Neg	FC	9.0	Pos	Neg	Neg	150.0	Neg	Neg

M: Male, F: Female, MNG: Multinodular goiter, PTC: Papillary thyroid carcinoma, V: Variant, FC: Follicular carcinoma, FA: Follicular adenoma, TA: Trabecular adenoma, HA: Hurthle cell adenoma, HC: Hurthle cell carcinoma, RAI: Radioactive iodine, WBS: Whole body scan, LN: Lymph node, Pos: Positive, Neg: Negative

linked pathogenesis compared to being purely coincidental. Furthermore, there is insufficient evidence of FC along with Hurthle cell/oncocyctic variants to suggest possible genetic linkage to such synchronicity (19).

## Conclusion

The synchronous occurrence of these neoplasms in a given patient is likely coincidental based on the current evidence in the literature. Further studies including a larger patient population with standardized genetic characterization are needed.

## Funding

We did not receive any funding from an organization during the design, data collection and analysis, decision to publish, or preparation of the manuscript

There is no conflict of interest declared by authors

## Acknowledgements

I wish to thank Dr. Cevdet Aydın and Didem Özdemir for the provision of follow up data.

## Ethics

*Ethics Committee Approval and Informed Consent: Ethical review board of Yıldırım Beyazıt University Atatürk Training and Research Hospital approved the study protocol.*

*Peer-Review: Externally peer-reviewed.*

## Authorship Contributions

*Surgical and Medical Practices: Şefika Burçak Polat, Aylin Yazgan, Mehmet Kılıç, Concept: Şefika Burçak Polat, Dilek Arpacı, Bekir Çakır, Design: Şefika Burçak Polat, Dilek Arpacı, Hüsnüye Başer, Data collection and Processing: Hüsnüye Başer, Analysis or Interpretation: Şefika Burçak Polat, Hüsnüye Başer, Reyhan Ersoy, Mehmet Kılıç, Literature Search: Dilek Arpacı, Writing: Şefika Burçak Polat, Bekir Çakır.*

*Conflict of Interest: Authors declare that there is no conflict of interest.*

*Financial Disclosure: The authors declare that this study received no financial support.*

## References

1. Jameson JL. Minimizing unnecessary surgery for thyroid nodules. *N Engl J Med* 2012;367:765-767.
2. Hegedüs L. Clinical practice. The thyroid nodule. *N Engl J Med* 2004;351:1764-1771.
3. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2004;74:2913-2921.
4. Hawasli A, Rizzo P, Khoury H, McCaffrey JL. Can fine-needle aspiration biopsy of thyroid nodule help in determining the extent of surgery in follicular and Hurthle cell neoplasm at a community teaching institution? *Am Surg* 2002;68:907-910.
5. Cramer JD, Fu P, Harth KC, Margevicius S, Wilhelm SM. Analysis of the rising incidence of thyroid cancer using the Surveillance, Epidemiology and End Results national cancer data registry. *Surgery* 2010;148:1147-1152.
6. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995 (see comments). *Cancer* 1998;83:2638-2648.
7. Nilubol N, Zhang L, Kebebew E. Multivariate analysis of the relationship between male sex, disease-specific survival, and features of tumor aggressiveness in thyroid cancer of follicular cell origin. *Thyroid* 2013;23:695-702.
8. Gurkan E, Gurbuz Y, Tarkun I, Canturk Z, Cetinarslan B. Mixed medullary-papillary carcinoma of the thyroid: report of two cases and review of the literature. *Indian J Pathol Microbiol* 2014;57:598-602.
9. Matias-Guiu X, Caixas A, Costa I, Cabezas R, Prat J. Compound medullary-papillary carcinoma of the thyroid: true mixed versus collision tumour. *Histopathology* 1994;25:183-185.
10. Bhargava P, Gayathri KB. Synchronous occurrence of anaplastic, follicular and papillary carcinomas with follicular adenoma in thyroid gland. *Indian J Pathol Microbiol* 2011;54:414-415.
11. Stratakis CA, Courcoutsakis NA, Abati A, Filie A, Doppman JL, Carney JA, Shewkh T. Thyroid gland abnormalities in patients with the syndrome of spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas (Carney complex). *J Clin Endocrinol Metab* 1997;82:2037-2043.
12. Ishikawa Y, Sugano H, Matsumoto T, Furuichi Y, Miller RW, Goto M. Unusual features of thyroid carcinomas in Japanese patients with Werner syndrome and possible genotype-phenotype relations to cell type and race. *Cancer* 1999;85:1345-1352.
13. Wu CJ, Chen HL, Song YM, Sheu WH, Chen SH. Mixed medullary-follicular carcinoma and papillary carcinoma of the same thyroid. *Intern Med* 1998;37:955-957.
14. Ganguly R, Mitra S, Datta AK. Synchronous occurrence of anaplastic, follicular and papillary carcinomas with follicular adenoma in thyroid gland. *Indian J Pathol Microbiol* 2010;53:337-339.
15. Meinhard K, Michailov I. Simultaneous occurrence of medullary and papillary carcinoma in the same thyroid lobe. *Zentralbl Pathol* 1995;140:459-464.
16. Cupisti K, Raffel A, Ramp U, Wolf A, Donner A, Krausch M, Eisenberger CF, Knoefel WT. Synchronous occurrence of a follicular, papillary and medullary thyroid carcinoma in a recurrent goiter. *Endocr J* 2005;52:281-285.
17. Vasko V, Ferrand M, Di Cristofaro J, Carayon P, Henry JF, de Micco C. Specific pattern of RAS oncogene mutations in follicular thyroid tumors. *J Clin Endocrinol Metab* 2003;88:2745-2752.
18. Sobrinho-Simões M, Máximo V, Rocha AS, Trovisco V, Castro P, Preto A, Lima J, Soares P. Intragenic mutations in thyroid cancer. *Endocrinol Metab Clin North Am* 2008;37:333-362.
19. Nikiforov YE. RET/PTC rearrangement in thyroid tumors. *Endocr Pathol* 2002;13:3-16.
20. Fogelfeld L, Bauer TK, Schneider AB, Swartz JE, Zitman R. p53 gene mutations in radiation-induced thyroid cancer. *J Clin Endocrinol Metab* 1996;81:3039-3044.