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Cytologic Comparison Between Growing and Non-growing Benign Thyroid Nodules Evaluated Using Two Different Growth Criteria

İki Farklı Büyüme Kriterine Göre Büyüyen ve Büyümeyen Benign Nodüllerin Sitolojik Karşılaştırması

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Abstract

Objective: Thyroid nodules are frequent in the adult population. Thyroid fine-needle aspiration biopsy is performed for diagnosing cancerous nodules. It is suggested that biopsy-proven benign thyroid nodules should be followed up clinically, and if they grow, rebiopsy should be performed. However, certain growth criteria have not yet been defined.

Material and Methods: We retrospectively reviewed thyroid fine-needle aspiration records of all patients at Dokuz Eylül University Hospital between January 2006 and June 2009. The nodules that underwent second biopsies were evaluated using two different growth criteria: at least 50% increase in the nodule maximal diameter and 20% increase in at least two nodule dimensions with a minimal increase of 2 mm.

Results: From a total of 4217 thyroid nodules, we evaluated the cytological results of 117 benign thyroid nodules, which underwent follow-up biopsies. No significant difference was observed in the cytological results of the growing group (n:21), which had at least 50% increase in the maximal nodule diameter, and the non-growing group (n:96) (p=0.999). In addition, using the growth criteria of 20% increase in at least two nodule dimensions with a minimal increase of 2 mm, no significant difference was observed in the cytological results of the growing (n:47) and non-growing (n:70) benign thyroid nodules (p=0.700).

Conclusion: According to two different growth criteria, the growth of a benign nodule is not an additional risk factor for cancer.

Keywords: Thyroid nodule; nodule growth; thyroid fine-needle aspiration biopsy

Özet

Amaç: Tiroid nodülü erişkinlerde sık görülür. Tiroid ince iğne aspirasyon biyopsisi tiroid nodülünde kanser varlığını araştırmak amaçlı kullanılır. Biyopsi ile benign oldukları saptanan nodüllerin klinik olarak izlenmesi, büyüme tespit edildiğinde yeniden biyopsi alınması önerilmektedir. Fakat net bir büyüme kriteri belirlenmemiştir.

Gereç ve Yöntemler: Dokuz Eylül Üniversitesi Hastanesi'nde Ocak 2006-Haziran 2009 tarihleri arasında uygulanan TİİAB kayıtları geriye dönük olarak incelendi. İkinci bir TİİAB yapılmış olan benign nodüllerin izlemdeki büyümeleri iki farklı büyüme kriteri kullanılarak (en büyük nodül çapında %50 ve ya üzerinde artış, nodülün en az iki çapında -2 mm'den az olmamak üzere- %20 veya üzerinde artış) değerlendirildi.

Bulgular: İnce iğne aspirasyon biyopsisi yapılan 4217 tiroid nodülden izlem biyopsileri olan benign nodüller incelemeye alındı. İzlemde maximum çapta %50 ve üzerinde artışa göre büyüyenle (n: 21), bu kritere göre büyümeyen (n:96) benign nodüller incelendiğinde aralarında anlamlı sitolojik fark saptanmadı (p=0.999). Benzer şekilde nodülün en az iki çapında –iki mm'den az olmamak üzere %20 ve üzerinde boyut artışı saptanan nodüllerle (n:47), bu kritere göre büyümeyenler (n:70) arasında anlamlı sitolojik fark saptanmadı (p=0.700).

Sonuç: Çalışmada kullanılan iki farklı büyüme kriterine göre benign nodüllerin izlemde büyümesi kanser varlığı için ek risk oluşturmamıştır.

Anahtar kelimeler: Tiroid nodülü; nodül büyümesi; tiroid ince iğne aspirasyon biyopsisi

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Introduction

A thyroid nodule is a frequently observed health problem. Thyroid nodules can be detected in 4% of the population by palpation and in up to 67% by ultrasonography (1). Thyroid nodules are clinically crucial, as they have 5% to 10% probability of thyroid cancer (2). A clinical approach to thyroid nodules aims at detecting cancerous nodules. The simplest and safest method to screen thyroid cancer is thyroid fine-needle aspiration biopsy (TFNAB; 3).

It is recommended that benign nodules diagnosed by TFNAB should be followed up with physical examination and thyroid ultrasonography (3). One of the most crucial criteria to be assessed during follow-up is the nodule growth. Rebiopsy is recommended for a growing nodule, which was initially benign (3). However, studies have shown that benign nodules can also grow in their natural course (4–6). There is no consensus about the "growth" criteria of thyroid nodules. Several criteria were used to establish the nodule "growth" (>50% increase in the maximal dimension of the nodule, >15% increase in the nodule volume, >30% increase in the nodule volume, etc. (7). American Thyroid Association (ATA) has defined a 20% increase in at least two nodule dimensions with a minimal increase of 2 mm as an acceptable growth criterion (3). However, till date, no evidence exists that cancer risk increases in benign nodules growing at follow-up.

This study aimed to compare the TFNAB results of the growing nodules, which had initially benign cytology, with non-growing nodules. We used two different growth criteria (i.e., at least 50% increase in the nodule maximal diameter and 20% increase in at least two nodule dimensions with a minimal increase of 2 mm) to detect whether the cancer risk of nodules growing at follow-up increases compared with the ones that do not grow.

Material and Methods

We retrospectively reviewed all results of ultrasonography-guided fine-needle aspiration biopsies performed at Dokuz Eylül University Hospital between January 2006 and June 2009. We recorded nodules that had repeated biopsies. Age, sex, radiation history to the neck, additional malignancy history, thyroid surgery history, familial history, and thyrotrophin stimulating hormone (TSH) level of the patient and the dimensions of the nodules were recorded. The nodules which had repeated biopsies were classified as growing and non-growing. Growth classification and evaluation have been performed separately according to two different criteria (at least 50% increase in the nodule maximal diameter and 20% increase in at least two nodule dimensions with a minimal increase of 2 mm), as no consensus exists about the exact growth criteria of thyroid nodules.

The biopsy results were classified as benign, intermediate, or malign. Nodules that are Thy 2-3-4 according to Bethesda classification were classified as intermediate. The existence of surgical intervention toward the nodule after the second fine-needle aspiration biopsy was ascertained. If there was any surgical intervention, we recorded the pathological diagnosis of the nodule.

The study protocol was approved by the local ethics committee.

Statistical analysis was performed using SPSS V15.0, SPSS Inc., Chicago. Nominal data were evaluated using chi-square test; continuous variables were assessed using independent sample's t-test or Mann-Whitney U test. Logistic regression analysis was performed for assessing the independent impact of a specific variable on other parameters.

Results

We retrospectively analyzed 4217 thyroid nodule biopsies from 3202 patients at Dokuz Eylül University Hospital between January 2006 and June 2009 (Figure 1). The general characteristics of the nodules are summarized in Table 1.

Out of the initial benign nodules (3509), 117 nodules that had repeated biopsy were included in the statistical analysis. There were 47 growing and 70 non-growing nodules using the growth criteria of 20% increase in at least two nodule dimensions with a minimal increase of 2 mm (Group 1); and there were 21 growing and 96 non-growing nodules using the growth criteria of at least 50% increase in the nodule maximal diameter (Group 2).

Group 1

No difference was observed in terms of age, TSH, and the initial maximal diameter of the nodule between growing and non-growing groups (Table 2). Follow-up time was longer in the growing group than the non-growing group (2.76 ±1.30 years vs. 2.13 ±1.33 years, p = 0.050). In addition, no difference was observed in the cytological results of rebiopsies between the two

Table 1. Characteristics of the nodules that underwent thyroid fine needle aspiration biopsy between January 2006–June 2009.

Total number of nodules	4217
Number of females (%)	3463 (80.0%)
Age (years) mean±SD	53.62±13.16
Nodule maximal diameter before initial biopsy (mm) mean±SD	16.90±9.01
Serum TSH level before initial biopsy (μu/mL) median [minimum-maximum]	0.85 [<0.001-353]

groups (p=0.70). Two nodules with non-benign cytology in the growing group were operated; both nodules were defined as papillary thyroid cancer (PTC). A total of 5 nodules out of 45 nodules with benign cytology in the growing group were operated; 3 of these nodules were defined as PTC. There were five nodules with intermediate cytology in the non-growing group; three of these nodules were operated, and two PTC and one benign nodule were established (Table 3). All of the five nodules with benign cytology in the non-growing group had benign pathology after surgery.

In the linear regression model including age, sex, TSH level, and follow-up period, the follow-up period was 1.5 times high in the growing nodules (Table 4).

Group 2

No difference in terms of age and TSH levels was observed between the growing and non-growing groups. The non-growing group had higher initial diameter than the growing group (Table 2). In addition, no difference was observed in terms of cytological results between the growing and non-growing groups (p=0.999). In both groups, malign cytology result was not found. After the surgical excision of the nodule with intermediate cytology in the growing group, PTC was found. Out of the 20 growing nodules, which had benign cytology, three were operated and all of them had benign pathology. Furthermore, four nodules with intermediate cytology were excised surgically in the non-growing group, although PTC was detected in three of them (Table 3). In addition, seven of the non-growing nodules with benign cytology were operated, although three of them had PTC.

When the data were evaluated with linear regression analysis, age, sex, initial TSH level, and follow-up period were not associated with nodules, which grow according to Group 2 criteria (Table 5).

A total of seven malign and eight benign pathology results were found. The growth rate of benign nodules was 1.81 [-2, 35-12, 42] mm/year, and the growth rate of malign nodules was 1.21 [-1, 12-4, 44] mm/year.

Discussion

In this study, we retrospectively examined the rebiopsies of thyroid nodules. Considering the two different growth criteria, we did not find an increased rate of malignancy in growing, initially benign nodules.

The natural course of benign thyroid nodules is not completely understood. Although the growth of the benign nodule can be attributed to its natural course, most guidelines recommended rebiopsy to exclude malignancy in growing nodules (3). There were different growth criteria used for defining the nodule "growth." The rate of nodule growth differed when different growth criteria were used. Erdogan et al. reported the rates of nodule growth for different criteria (32% for ≥15% change in the nodule volume, 24.1% for ≥30% change in the nodule volume, and 4.1%

Table 2. Nodule characteristics.

	Group 1			Group 2		
	Growing (n=47)	Non-growing (n=70)	P	Growing (n=21)	Non-growing (n=96)	P
Age (year)	52.94±11.73	55.64±12.05	0.231	54.81±11.99	54.5±11.99	0.943
Maximal Diameter of the Nodule (mm)	15.38±6.39	17.60±6.25	0.065	12.00±5.05	17.74±6.18	0.013
TSH (μU/mL)	1.23±1.70	1.38±1.42	0.625	1.71±2.36	1.23±1.28	0.495
Follow up Time (year)	2.76 ±1.30	2.13 ±1.33	0.050	2.31 ±1.15	2.40 ±1.39	0.969
Growth Speed (mm/year)	3.2 ±2.87	0.37 ±3.5	0.009	5.83 ±4.88	0.59 ±2.42	0.011

Group 1: 20% increase in at least two nodule dimensions with a minimal increase of 2 mm.
Group 2: At least 50% increase in nodule maximal diameter.

Table 3. Characteristics of cytology and pathology of growing and nongrowing nodules.

	Cytology (n)	Pathology (n)
Group 1 Growing (N= 47)	Benign: 45	Benign: 2
		PTC: 3
	Intermediate: 2	Benign: 0
		PTC:2
Group 1 Nongrowing (N=70)	Benign: 65	Benign: 5
		PTC: 0
	Intermediate: 5	Benign:1
		PTC: 2
Group 2 Growing (N=21)	Benign:20	Benign:3
		PTC:0
	Intermediate: 1	Benign:0
		PTC:1
Group 2 Nongrowing (N=96)	Benign: 90	Benign:4
		PTC:3
	Intermediate: 6	Benign:1
		PTC:3

Group 1: 20% increase in at least two nodule dimensions with a minimal increase of 2 mm.
Group 2: At least 50% increase in nodule maximal diameter.
PTC: Papillary thyroid cancer.

Table 4. Factors predicting "20% increase in at least two nodule dimensions with a minimal increase of 2 mm".

	ODDS ratio	95% CI	p-value
Age	0.967	0.93-1.01	0.100
Sex	1.240	0.38-4.10	0.724
Follow-up period	1.537	1.07-2.20	0.023*
TSH	0.921	0.68-1.24	0.588

*p<0.05.

Table 5. Factors predicting at least 50% increase in nodule maximal diameter.

	ODDS ratio	95% CI	p-value
Age	0.99	0.95-1.04	0.810
Sex	0.554	0.11-2.83	0.478
Follow-up period	1.023	0.66-1.60	0.920
TSH	1.157	0.86-1.56	0.333

for ≥50% change in the maximal diameter of the nodule; 7). Lim et al. reported that 11.8% and 9.4% of benign nodules grew using ≥50% increase in volume and ≥20% increase in at least two nodule dimensions with a minimal increase of 2 mm as a cut-off value, respectively (8).
ATA recommended the rebiopsy of initially benign nodules if ≥20% increase was observed in at least two nodule dimensions with a minimal increase of 2 mm (3). Durante et al. reported that 15.4% (n=153) of the benign nodules grew using the ATA criteria (9). Only two malignancies were detected from these nodules after second TFNAB. Rosario et al. reported the rebiopsy results of the initial benign nodules (10). Out of 86 growing nodules (using ATA criteria), only three malignancies (3.5%) were detected after the second biopsy. In addition, Kim et al. reported a growth rate of 21.1% considering the criteria of 50% change in the nodule volume (11). Moreover, they found only one malignancy among 172 growing nodules. The results of all these studies suggested that a proportion of benign nodules grow over time and the malignancy rate of these growing nodules in follow-up is very low.
In a recent study, malign nodules were found more likely to grow more than 2 mm/year compared with benign nodules (12). As a limited number of patients had final pathology in our study, no difference was observed between benign and malign nodules in terms of nodule growth speed. In addition, the follow-up time for growing nodules was longer than that for non-growing nodules in Group 1. No data exist in the literature comparing the follow-up time and growth; therefore, additional studies are required to interpret this finding.
We have found intermediate cytological results in growing and non-growing nodules during follow-up. The reason for changing the cytological characteristics of the nodules may be the false negative rate of the initial TFNAB rather than that the growth in follow-up increases the malignancy risk. As in a study in which growth has not been used as a criterion and the rebiopsies of benign nodules during follow-up have been examined, rebiopsies in 13.2% of benign nodules showed intermediate or malign cytology (13). Similarly, in another study including the rebiopsies of benign nodules with suspicious ultrasonographic features, in 17.4% of them, suspicious cytology was found (14). Therefore, in some studies, TFNAB is recommended for benign thyroid nodules in follow-up (15).
We faced various limitations during our study. First, a retrospective approach weakens the strength of the study. In this study, we used the biopsies from non-growing nodules as a control group. However, data were not available indicating the reason for taking a biopsy from the non-growing nodules during follow-up. Repeated biopsy may have been taken from a group with

high clinical cancer suspicion even there was no dimensional growth. Therefore, the control group may be a group with high risk. Intermediate risk category is a very heterogeneous group, and possible discordance between the cytologists is another limitation.

Conclusions and Recommendations

The most outstanding clinical importance of thyroid nodule is a cancer risk. In this study, two different growth criteria were used, and it was observed that the cancer risk of growing benign nodules was not higher than the non-growing ones. It is necessary that these findings are supported by broad and prospective studies.

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Authorship Contributions

Idea/Concept: Mehmet Muhittin Yalçın, Sena Yeşil, Barış Akıncı; Design: Mehmet Muhittin Yalçın, Barış Akıncı, Abdurrahman Çömlekci, Fırat Bayraktar; Control/Supervision: Abdurrahman Çömlekci, Fırat Bayraktar, Sevinç Eraslan, Aytaç Gülcü, Tülay Canda; Data Collection and/or Processing: Mehmet Muhittin Yalçın, Sinan Ünal; Analysis and/or Interpretation: Mehmet Muhittin Yalçın, Barış Akıncı, Sena Yeşi; Literature Review: Mehmet Muhittin Yalçın, Barış Akıncı, Sena Yeşil; Writing the Article: Mehmet Muhittin Yalçın, Barış Akıncı; Critical Review: Abdurrahman Çömlekci, Fırat Bayraktar, Sevinç Eraslan, Aytaç Gülcü, Tülay Canda; References and Fundings: Abdurrahman Çömlekci, Fırat Bayraktar, Sevinç Eraslan.

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