Would high body mass index and TSH level affect selecting thyroid nodule for fine-needle aspiration biopsy?

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Would high body mass index and TSH level affect selecting thyroid nodule for fine-needle aspiration biopsy?

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ABSTRACT

Would high body mass index and TSH level affect selecting thyroid nodule for fine-needle aspiration biopsy?

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Purpose

The purpose of this study was to evaluate whether high body mass index (BMI) or thyroid stimulating hormone (TSH) level would affect selecting thyroid nodule for fine-needle aspiration biopsy (FNA).

Materials and Methods

Among thyroid nodules that were biopsied in our institution from February 2006 to December 2008, 3,155 thyroid nodules with 5 mm or larger, in patients without medication history, and with BMI and TSH values and cytopathologic results were selected. Four grades of BMI were applied (underweight, <18.5; normal, 18.5 - 24.9; overweight, 25 - 29.9; obese, ≥30) and TSH levels were classified into low, normal, and high. Ultrasound (US) features of the thyroid nodules were divided into ‘probably benign’ and ‘suspicious for malignancy’ categories. Univariate and multivariate logistic regression analysis were used to find the association between variables and malignancy. We tested interactions

on a multiplicative scale to evaluate whether the associations between BMI grade and malignancy is different by age group or gender.

Results

The grades of BMI showed difference between malignant and non-malignant groups (P = .016). The TSH levels were significantly different between the malignant and non-malignant groups (P < .001) showing higher percentage of high TSH level among malignant group (22.0%) compared to non-malignant group (11.4%). Multivariate analysis showed no significant association between high BMI and malignancy. Thyroid malignancy showed significant association with 'suspicious for malignancy' US category (OR = 1.883, P < .001) and high TSH level (OR = 1.095, P < .001). High TSH level showed significant association with malignancy in nodules with 'suspicious for malignancy' US category (OR = 1.178, P < .001), but not in nodules with 'probably benign' US category (OR = 1.022, P = .281). On multivariate analysis according to age groups, being obese from the ages of 60 to 69 years were significantly associated with a malignancy (OR = 1.173, P = .033).

Conclusion

High BMI and TSH level did not give additional information for selecting thyroid nodule for FNA with US. However, being obese in late adulthood was significantly associated with malignancy.

Key words: thyroid nodule, thyroid cancer, ultrasound, body mass index, thyroid stimulating hormone, fine-needle aspiration biopsy

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I. INTRODUCTION

Thyroid cancer incidence has been sharply increasing worldwide in the last few years period [1-3]. This is partially due to medical surveillance and widespread use of highly sensitive diagnostic tools such as ultrasound (US) and fine-needle aspiration biopsy (FNA) [3]. However, the increase incidence of large papillary thyroid cancer cannot be explained alone by the widespread of the sensitive diagnostic tool [4].

Including ionizing radiation [5], there are many other potential risk factors for thyroid cancer such as history of thyroid cancer in first degree relatives, ionizing radiation, prior history of thyroid cancer, and high calcitonin level [6]. Recently, obesity has been raised as another potential risk factor for thyroid cancer as there was a dramatic increase of both thyroid cancer and the prevalence of obesity in the similar period [4,7]. Up to present, the best level of evidence is derived from a pooled analysis of prospective studies (n = 848,932) showing that obesity is an independent risk factor for thyroid cancer (HR 1.21 in men and 1.16 in women) [8]. This was also true on health checkup setting with

15,068 subjects and with FNA results of 1,427 patients; the prevalence of thyroid cancer in women was associated with a high body mass index (BMI), per 5 kg/m^2 increase (OR, 1.63, $P < .001$) [9]. Addition to high BMI, high thyroid stimulating hormone (TSH) level was reported to be a risk factor for a malignant thyroid nodule [10,11]. There was positive association between BMI and TSH level in studied including euthyroid patients [12-14] as well as hypothyroidism patients [15,16].

The most important factor that determines the need for FNA is the size and the US feature of the thyroid nodule. Suspicious US feature includes the following; micro or macrocalcification, irregular or microlobulated margin, taller than wide shape, abnormally increased vascularity, hypoechogenicity or marked hypoechogenicity, and solidity [6,17-19]. Until now, none of the studies have evaluated the association of high BMI or TSH level with thyroid malignancy after adjusting US features and it remains unclear whether the potential risk factors would affect selecting a nodule for FNA. Therefore, the purpose of this study was to evaluate whether high BMI or TSH level would affect selecting thyroid nodule for FNA which is an essential procedure followed by adequate choice of treatment, and see if there is any different effect by gender and age.

II. MATERIALS AND METHODS

This retrospective study was approved by the institutional review board, and the informed consent was waived. Informed consent for the

US-guided FNA was obtained from all patients prior to each biopsy.

1. Study population

Among thyroid nodules that were biopsied in our institution from February 2006 through December 2008, we selected the nodules with following criteria making 3,720 nodules included; nodules 5 mm or larger, in patients without thyroid hormone medication history, and in patients with height, weight, and TSH values in the medical records within three months from the day of FNA. The 543 nodules in 536 patients were excluded due to lack of definitive cytologic or further pathologic diagnosis following surgery. Finally, 3,155 nodules in 2,974 patients made up the study population.

2. Data acquisition and patient grouping

Clinical information was systematically abstracted and collected from patients' electronic medical records by a 4^{th} year resident and a trained person who worked in our radiology department for 5 years. The patients included in this study had available records of the height, weight, and serum TSH levels on the each day of outpatient clinic visit within three months from the day of FNA.

The BMI was calculated (weight (kg)/height $(m)^2$) using each patient's height and weight. Patients were assigned into four grades according to BMI using the World Health Organization classification; underweight with BMI < 18.5; normal with BMI 18.5 to 24.9; overweight with BMI 25 to 29.9, and

obese with BMI ≥30 [20]. The patients were also classified into seven groups according to their age; less than 20, 20 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, and 70 years or older. Serum TSH levels were determined by radioimmunoassay (Trinity Biotech, Co. Wicklow, Ireland, reference range 0.4–3.1 μIU/mL) or IRMA (TSH-CTK-3, SORIN Biomedica, Saluggia, Italy, reference range 0.3–4.99 μIU/mL). The TSH values were classified into three levels, low (lower than reference range), normal (within reference range), and high (higher than reference range).

3. Ultrasound evaluation and ultrasound-guided FNA

Images of US were obtained using 5–12-MHz linear transducers (HDI 5000 and IU-22, respectively; Philips, Bothell, WA). Ultrasound features of the thyroid nodules that underwent US-guided FNA were recorded according to internal component, echogenicity, margin, calcification, shape, and vascularity (Appendix 1). Based on the US features, thyroid nodules were divided into two categories, 'probably benign' and 'suspicious for malignancy'. If there is one or more suspicious US feature, the thyroid nodule was described 'suspicious for malignancy' [21].

For FNA, a 23-gauge needle attached to a 2-mL or 20-mL disposable plastic syringe was used. In each nodule, aspiration was done twice or more times and aspirated materials were expelled onto glass slides followed by smearing. All smeared glass slides were placed in 95% alcohol for Papanicolaou

staining and the remaining material was rinsed in saline solution. Cytologic evaluation at the site of FNA procedure was not done in our institution. After the glass sides of expelled aspirated material were moved to the pathologic department, the slides were interpreted by five experienced cytopathologists. In the study period, cytological reports were categorized as 'benign', 'indeterminate', 'suspicious for papillary thyroid carcinoma', 'malignant', or 'nondiagnostic' [22-25]. Definitive cytologic result for analysis included 'benign' and 'malignant'.

4. Statistical analysis

Two sample t-tests were used to compare continuous variables including nodule size, height, and weight of patients in the malignant and non-malignant nodule groups. Chi-square test was used to compare categorical variables including gender, BMI grade, TSH level, and US category in the two groups. Age was analyzed as both a continuous and categorical variable.

The odds ratio (OR) with 95% confidence intervals (CI) of malignancy for each clinical and US features was calculated with univariate and multivariate logistic regression analysis. As some of the previous study showed positive association between BMI and TSH level, we analyzed the association between the two [13,14]. The association between BMI and TSH values were evaluated using ANOVA and there was no statistical association between the two (P = .354). Therefore, we included both BMI value and TSH level as

independent variables in multiple logistic regression analysis. After adjusting for all factors in the univariate analysis except height and weight, which were used calculating BMI, multiple logistic regression analysis was performed to assess independent associations of a thyroid malignancy with all clinical factors and US categories. To evaluate the effect of clinical factors on the selecting nodule for FNA, univariate and multivariate logistic regression analysis was done in nodules with each US category. We used logistic regression with generalized estimating equation.

To evaluate whether the associations between age groups or gender and malignancy were affected by the grade of BMI, we tested their interactions on a multiplicative scale. Specifically, the logistic regression models included the interaction term for age groups x BMI grades and gender x BMI grades, respectively. Subsequently, the ORs and 95% CIs of malignant thyroid nodule in association with BMI at each age period were estimated using univariate and multivariate logistic regression with adjustment for all the clinical factors and US features. The SAS ver. 9.2 (SAS Inc., Cary, NC, USA) was used for statistical analysis. A *P* value less than 0.15 was considered significant for multiplicative interaction [26] and that less than 0.05 was considered significant for other statistical analysis.

III. RESULTS

Clinical factors and US category of 3,155 nodules according to the malignant or non-malignant nodule groups were shown in Table 1. Patients with

malignant nodules were significantly younger compared to patients with non-malignant nodules ($P < .001$). Malignant nodules had significantly smaller size ($P < .001$). The grades of BMI showed difference between malignant and non-malignant groups ($P = .016$). The TSH levels were significantly different between the malignant and non-malignant groups ($P < .001$) showing higher percentage of high TSH level among malignant group (22.0%) compared to non-malignant group (11.4%). The 'suspicious for malignancy' US category was significantly more frequent in malignant group compared to non-malignant group (86.4% vs. 14.7%; $P < .001$).

Table 1. Baseline characteristics of 3155 thyroid nodules in 2974 patients

Variable	Total (n=3155)	Non-malignant nodule (n=2159)	Malignant nodule (n=996)	*P*-value
Age, years	51.4±12.1	52.9±11.6	48.1±12.4	<.001
<45	817 (25.9)	452 (20.9)	365 (36.7)	<.001
≥45	2338 (74.1)	1707 (79.1)	631 (63.4)	
Gender				0.218
Male	492 (15.6)	325 (15.1)	167 (16.8)	
Female	2663 (84.4)	1834 (85.0)	829 (83.2)	
Nodule size, mm	15.8±11.0	17.3±11.6	12.6±8.7	<.001
BMI grade (kg/m^2)				
Underweight (<18.5)	118 (3.7)	71 (3.3)	47 (4.7)	0.016
Normal (18.5~24.9)	2083 (66.0)	1454 (67.4)	629 (63.2)	
Overweight (25~29.9)	852 (27.0)	574 (26.6)	278 (27.9)	
Obese (≥30)	10 (3.2)	60 (2.8)	42 (4.2)	
TSH				<.001
Low	213 (6.8)	201 (9.3)	12 (1.2)	
Normal	2478 (78.5)	1713 (79.3)	765 (76.8)	
High	464 (14.7)	245 (11.4)	219 (22.0)	
US category				<.001
Probably benign	1977 (62.7)	1841 (85.3)	136 (13.7)	
Suspicious for malignancy	1178 (37.3)	318 (14.7)	860 (86.4)	

Note - percentages in parentheses; BMI, body mass index; TSH, thyroid stimulating hormone; US, ultrasound

Multivariate logistic regression showed high TSH level (OR = 1.095, *P* < .001) and 'suspicious for malignancy' US category (OR = 1.883, *P* < .001) were significantly associated with malignant thyroid nodules (Table 2). Younger age (OR = 1.005, *P* < .001) and male gender (OR = 1.038, *P* = .019) had also significant association with malignant thyroid nodules on multivariate logistic regression analysis.

Table 2. Univariate and multivariate analysis of association between thyroid malignancy and clinical and imaging features

Variable	Univariate		Multivariate	
	OR(95% CI)	*P*-value	OR(95% CI)	*P*-value
Age, years	0.993(0.992-0.994)	<.001	0.995(0.994-0.996)	<.001
<45	1.193(1.148-1.242)	<.001		
≥45	reference			
Gender				
Male	1.029(0.981-1.079)	0.245	1.038(1.006-1.070)	0.019
Female	reference		reference	
Nodule size	0.992(0.990-0.993)	<.001	0.999(0.998-1.000)	0.064
Height	1.003(1.001-1.006)	0.008		
Weight	1.002(1.000-1.004)	0.030		
BMI grade (kg/m^2)	1.002(0.997-1.008)	0.405		
Underweight (<18.5)	1.101(1.003-1.209)	0.044	1.039(0.975-1.107)	0.241
Normal (18.5~24.9)	reference		reference	
Overweight (25~29.9)	1.025(0.985-1.066)	0.224	1.010(0.982-1.039)	0.485
Obese (≥30)	1.116(1.006-1.238)	0.037	1.058(0.985-1.136)	0.123
TSH				
Low	0.777(0.749-0.806)	<.001	0.892(0.857-0.928)	<.001
Normal	reference		reference	
High	1.177(1.119-1.239)	<.001	1.095(1.059-1.132)	<.001
US category				
Probably benign	reference			
Suspicious for malignancy	1.937(1.883-1.993)	<.001	1.883(1.828-1.94)	<.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; TSH, thyroid stimulating hormone; US, ultrasound

Multivariate logistic regression analysis in each of US category is shown in Table 3. In nodules with 'probably benign' US category, neither high BMI (overweight; OR = 1.008, *P* = .566 and obese; OR = 1.036, *P* = .364) nor high TSH level (OR = 1.022, *P* = .281) were significantly associated with malignancy. However, in nodules with 'suspicious for malignancy' US category, high TSH level was significantly associated with malignancy (OR = 1.178, *P* < .001). Regardless of the US category, low TSH level was significantly association with decreased risk of malignancy ('probably benign' US category; OR = 0.956, *P* < .001 and 'suspicious for malignancy' US category; OR = 0.656, *P* < .001) on multivariate logistic regression analysis.

Table 3. Multivariate analysis of association between thyroid malignancy and clinical and imaging features according to ultrasound category

Variable	'Probably benign' Ultrasound category		'Suspicious for malignancy' Ultrasound category	
	OR(95% CI)	*P*-value	OR(95% CI)	*P*-value
Age	0.997(0.996-0.998)	<.001	0.992(0.990-0.994)	<.001
Gender				
Male	1.009(0.979-1.041)	0.560	1.078(1.011-1.149)	0.021
Female	reference		reference	
Nodule size	0.999(0.998-0.999)	0.003	1.000(0.997-1.003)	0.957
Height				
Weight				
BMI grade (kg/m^2)				
Underweight (<18.5)	1.030(0.957-1.110)	0.432	1.043(0.930-1.171)	0.470
Normal (18.5~24.9)	reference		reference	
Overweight (25~29.9)	1.008(0.982-1.034)	0.566	1.006(0.949-1.065)	0.852
Obese (≥30)	1.036(0.960-1.119)	0.364	1.071(0.949-1.209)	0.264
TSH				
Low	0.956(0.936-0.976)	<.001	0.656(0.571-0.754)	<.001
Normal	reference		reference	
High	1.022(0.983-1.062)	0.281	1.178(1.117-1.242)	<.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; TSH, thyroid stimulating hormone

For predicting a thyroid malignancy, there were significant interactions between BMI and age group (*P-interaction* = .117) and no significant interactions between BMI and gender (*P-interaction* = .173). Therefore, we evaluated independent risk factors for a thyroid malignancy according to the age group. On multivariate analysis, BMI grade obese from the ages of 60 to 69 years were significantly associated with thyroid malignancy (OR = 1.173, *P* = .033) (Table 4).

Table 4. Association between thyroid malignancy and BMI grade obese (≥ 30 kg/m^2) by different age groups

BMI grade obese (≥ 30 kg/m^2) vs. non-obese (BMI < 30 kg/m^2)								
Age (year)	Non-malignant		Malignant		Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
	Obese	Non-obese	Obese	Non-obese				
- 20	0	9	0	10				
20 - 30	2	64	1	61	0.857(0.499-1.472)	0.575	0.720(0.500-1.038)	0.078
30 - 40	7	189	6	171	0.987(0.732-1.33)	0.930	0.949(0.771-1.169)	0.623
40 -50	13	502	9	276	1.056(0.846-1.318)	0.631	0.989(0.859-1.140)	0.883
50 - 60	18	696	11	259	1.114(0.928-1.338)	0.246	1.038(0.945-1.140)	0.435
60 - 70	17	507	12	139	1.220(1.008-1.476)	0.041	1.173(1.013-1.359)	0.033
70 -	3	132	3	38	1.319(0.827-2.102)	0.246	1.160(0.814-1.653)	0.411

BMI, body mass index; OR, odds ratio; CI, confidence interval

IV. DISCUSSION

In this study, a malignant thyroid nodule was significantly associated with high TSH level but not with high BMI on multivariate analysis. The Revised American Thyroid Association guideline recommends FNA at a thyroid nodule which is larger than 5 mm with suspicious US features [5]. When we evaluated the association of a thyroid malignancy with high TSH or BMI according to the US category, neither high BMI nor high TSH level were significantly associated with malignancy in nodules with ‘probably benign’ US

category. In contrast, high TSH level, not high BMI, was significantly associated with malignancy in nodules with ‘suspicious for malignancy’ US category. Therefore, high TSH level does not have additional value to select a thyroid nodule which should be aspirated because it was a significant independent factor for predicting a malignancy only in a thyroid nodule with suspicious US feature not in one without suspicious US feature. The results are important because, to date, although the significant associations between malignancy and high BMI or TSH level have been studied, there was no study showing whether different approach is needed for obese patients when performing FNA.

Before multivariate analysis for evaluating several clinical factors and malignant thyroid nodules, we performed the interaction test between TSH and BMI because high BMI and TSH level have been showing positive association with thyroid malignancy [12-14]. It is well known that TSH is related to energy metabolism of body [27], and may be due to higher prevalence of hypothyroidism in obesity, there were early studies showing increased TSH levels in patients with high BMI [16,28]. However, in our study, there was no significant association between BMI and TSH levels, i.e., increasing BMI and high TSH level did not show significant association. Therefore, it was possible to include both BMI grade and TSH level as confounding factors for multivariate analysis to see the association with malignant thyroid nodule.

There were studies showing different association between BMI and

thyroid cancer by age with more significance revealed in younger age group [8,29,30], though not all [31]. Due to the significant interactions between BMI and age group for predicting a thyroid malignancy, we investigated independent risk factors for diagnosing a thyroid malignancy according to age groups. Obesity in 60 to 69 years-old patients was significantly associated with a malignant thyroid nodule after adjusting all clinical and US features. This is a result that needs attention because it suggests that obese old adults are in greater risk of thyroid cancer than in younger adults.

In addition, the association between BMI and thyroid cancer can be different by gender, as several reports showing positive association only in women but not in men [9,30]. However, a pooled analysis of five prospective studies showed no significant difference by gender [8]. Comparable to this study, interaction between BMI and gender was not significant for predicting thyroid malignancy in our results.

There were some limitations to our study. First, there is inevitable selection bias in our study. If the patient did not undergo operation after FNA with inconclusive cytological result (indeterminate, suspicious for papillary thyroid carcinoma, or nondiagnostic), those nodules have been excluded from the study subjects. Second, there is possibility of false-negative or false-positive results for the thyroid nodules, as we included FNA cytological results, not surgical pathology, of malignant and benign. However, we cannot attribute the potential misinterpretation of the results to the false results on FNA, as the

previous studies conducted in our institution showed relatively low rate of false-negative or false-positive results [23,32]. Third, there was relatively small number of obese patients (3.2%, n = 102) in our study population, which may limit the assessment of the hazards of the various factors. Different result may come out in other study population with higher proportion of obese group like in western countries. Lastly, we did not obtain data on the exposures such as cigarette smoking, alcohol intake, physical activity, and medical history of diabetes which could be more related to the older age group than the younger group. Additional adjustment for these factors could have influenced on the results.

V. CONCLUSION

Although there were more malignant thyroid nodules in patients with high BMI or TSH level, those were not significant factors determining thyroid nodule for FNA additional to US features. Still, being obese in late adulthood was significantly associated malignancy, leading to a need for further study with large sample size.

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APPENDICES

In our institution, the echogenicity of thyroid nodules was classified as followings; hyperechogenic (hyperechogenic compared to the normal thyroid gland), isoechogenic (isoechogenic compared to the normal thyroid gland), hypoechogenic (hypoechogenic compared to the normal thyroid gland but hyperechogenic to the surrounding strap muscle), and marked hypoechogenic (hypoechogenic compared to the surrounding strap muscle). The classification of nodules' margin includes well-circumscribed, microlobulated, and irregular. The classification of calcification are microcalcification (calcification less than 1 mm), macrocalcification (calcification 1 mm or larger), eggshell calcification, and no calcification. The shape of nodules was classified as wider than tall (transverse diameter to the anteroposterior diameter ratio < 1) and taller than wide (transverse diameter to the anteroposterior diameter ratio ≥ 1) [33]. It was considered suspicious for malignancy if there us one or more of the above suspicious US features. Nodules with no suspicious US feature was considered probably benign nodule.

ABSTRACT(IN KOREAN)

높은 신체질량지수와 갑상선 자극 호르몬 수치가 갑상선 결절의 미세바늘흡인생검 결정에 영향을 미칠 것인가?

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목적

이 논문의 목적은 신체질량지수나 갑상선 자극 호르몬 수치가 미세바늘흡인생검 여부를 결정하는데 영향을 미치는지를 알아보는 것이다.

재료 및 방법

2006년 2월부터 2008년 12월까지 본원에서 미세바늘흡인생검을 받은 갑상선 결절 중 크기가 5 mm 이상이며, 약물 치료를 받은 적이 없고, 신체질량지수, 갑상선 자극 호르몬 수치, 그리고 조직검사 결과를 얻을 수 있는 환자의 결절 3,155개를 선택하였다. 신체질량지수는 네 단계로 구분되었고 (1 단계, <18.5; 2 단계, 18.5 – 24.9; 3 단계, 25 – 29.9; 4 단계, ≥30) 갑상선 자극 호르몬 수치는 세 단계로 구분되었다 (낮음, 정상, 높음). 초음파 소견에 따라 갑상선 결절들은 '양성 추정'과 '악성 의증'으로 구분되었다. 환자들은 나이에 따라 20세 미만부터 70세 이상까지 10세 별로 나누어 졌다. 단변량과 다변량 분석으로 변수와 악성 결절과의 연관성을 분석하였다. 신체질량지수의 단계와 악성과의 연관성이 나이나 성별 별로 차이가 있는지 확인하기 위해 상호작용 분석을 시행하였다.

결과

악성과 양성 결절간에 신체질량지수 단계의 차이가 있었다 (P = .016). 악성과 양성 결절간에 갑상선 자극 호르몬 수치에 차이가 있었으며

(P < .001) 높은 갑상선 자극 호르몬 수치의 비율이 양성 결절보다 (11.4%) 악성 결절에서 (22.0%) 더 높았다. 다변량 분석을 했을 때 악성 결절과 높은 신체질량지수는 유의한 연관성이 없었지만 '악성 의증' 초음파 소견과 (OR = 1.883, P < .001) 높은 갑상선 자극 호르몬 수치와는 (OR = 1.095, P < .001) 유의한 연관성이 있었다. '악성 의증' 초음파 소견을 보인 갑상선 결절들에서는 높은 갑상선 자극 호르몬 수치는 악성과 유의한 연관성을 보이지만 (OR = 1.178, P < .001) '양성 추정' 초음파 소견을 보인 갑상선 결절들에서는 유의한 연관성이 없었다 (OR = 1.022, P = .281). 나이에 따른 다변량 분석을 시행하였을 때 60에서 69세 환자들에서는 신체질량지수 4 단계와 악성이 유의한 연관성이 있었다 (OR = 1.173, P = .033)

결론

미세바늘흡인생검을 위한 결절을 선택할 때 높은 신체질량지수와 갑상선 자극 호르몬 수치는 중요한 정보를 제공하지 않는다. 하지만 노년기에서의 비만은 갑상선 암과 유의한 연관성이 있었다.

핵심되는 말 : 갑상선 결절, 갑상선 암, 초음파, 신체질량지수, 갑상선 자극 호르몬, 미세바늘흡인생검