

ลักษณะทางคลินิกและผลพยาธิวิทยาของก้อนเดี่ยวของต่อมไทรอยด์ในโรงพยาบาลตรัง

รุ่งโรจน์ ตั้งสถิตพร

Clinical and Pathological Characteristics of Solitary Thyroid Nodules in Trang Hospital.

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บทคัดย่อ:

วัตถุประสงค์: เพื่อศึกษาลักษณะทางคลินิก ผลทางพยาธิวิทยา ในผู้ป่วยก้อนเดี่ยวของต่อมไทรอยด์ที่ได้รับการผ่าตัดในโรงพยาบาลตรัง และพัฒนาแนวทางในการดูแลรักษาผู้ป่วยก้อนเดี่ยวของต่อมไทรอยด์ที่เหมาะสมกับโรงพยาบาลตรัง

วัสดุและวิธีการวิจัย: ศึกษาแบบพรรณนาเชิงย้อนหลัง โดยเก็บข้อมูลผู้ป่วยที่ได้รับการวินิจฉัยเป็นก้อนเดี่ยวของต่อมไทรอยด์ ที่ได้รับการผ่าตัดในโรงพยาบาลตรัง ระหว่าง มกราคม พ.ศ. 2545 ถึง กันยายน พ.ศ. 2553 โดยรวบรวมข้อมูลจากเวชระเบียน บันทึกการผ่าตัดและผลการตรวจทางพยาธิวิทยา แล้วนำข้อมูลที่ได้มาวิเคราะห์ค่าต่างๆ ทางสถิติ

ผลการศึกษา: มีผู้ป่วยทั้งสิ้น 620 ราย เป็นชายต่อหญิงในอัตราส่วนเท่ากับ 1: 11.5 อายุเฉลี่ย 40.5 ปี ผู้ป่วยที่ได้รับการผ่าตัดอยู่ในช่วงอายุ 31-40 ปีมากที่สุด ระยะเวลาการเป็นโรคโดยเฉลี่ย 28.3 เดือน ก่อนที่ได้รับการผ่าตัด มีขนาดเฉลี่ย 2.8 เซนติเมตร ผู้ป่วยที่ได้รับการเจาะเลือด พบว่าร้อยละ 89 มีค่าการทำงานของต่อมไทรอยด์ปกติ ผู้ป่วยส่วนใหญ่ได้รับการเจาะดูดก้อนเนื้อของต่อมไทรอยด์เพื่อตรวจทางเซลล์วิทยา ผลที่ได้มีค่า likelihood ratio 14.8 เมื่อผลตรวจสงสัยหรือพบเซลล์มะเร็ง การตรวจทางพยาธิวิทยา พบผลที่ไม่ใช่มะเร็งร้อยละ 78.1 ส่วนใหญ่เป็นคอกพอกธรรมดา ผลเป็นมะเร็งร้อยละ 21.9 ส่วนใหญ่เป็นมะเร็งชนิด well differentiated ผู้ป่วยกลุ่มอายุตั้งแต่ 30 ปีลงมา ผู้ป่วยที่มีค่าการทำงานของต่อมไทรอยด์ต่ำกว่าปกติ มีความเสี่ยงที่จะเป็นมะเร็งมากกว่ากลุ่มอื่นอย่างมีนัยสำคัญ

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สรุป: ผู้ป่วยก้อนเดี่ยวของต่อมไทรอยด์ส่วนใหญ่มีผลทางพยาธิวิทยาที่ไม่ใช่มะเร็ง การมีแนวทางการดูแลรักษาที่ดีและเหมาะสมร่วมกับการตรวจทางเซลล์วิทยา สามารถช่วยให้ลดการผ่าตัดในรายที่ไม่จำเป็น

คำสำคัญ: ก้อนเดี่ยวของต่อมไทรอยด์

Abstract:

Objective: To study clinical features and pathological results of patients with solitary thyroid nodules that underwent surgery in Trang Hospital and develop a management guideline for setting of Trang Hospital.

Materials and methods: A retrospective descriptive study. Medical records of patient with solitary thyroid nodule that underwent surgery in Trang Hospital during January 2002 to September 2010 were reviewed. Demographic data, clinical, laboratory and pathological findings were collected and data were analyzed.

Results: Total of 620 patients were included in the study with male to female ratio of 1:11.5. The average age was 40.5 years. Most patients were in age group of 31-40 years. The average duration of disease was 28.3 months. The average size of nodules was 2.8 cm. Eighty-nine percent of patients that had a thyroid function test were euthyroid. Most patients had fine needle aspiration cytology (FNAC) before surgery, FNAC results had likelihood ratio of 14.8 for prediction of malignancy. Seventy-eight point one percent of pathological results were benign and 21.9% were malignant. Nodular goiter was the most common in benign lesions, while well-differentiated cancer was the most common in malignant lesions. Risk of malignancy was significantly high in patients with age of 30 years or less, or with hypothyroid than other groups.

Conclusions: Most of solitary thyroid nodules are benign and can be treated conservatively. A thorough clinical assessment along with FNAC can avoid unnecessary operation.

Key words: solitary thyroid nodule

Introduction

A thyroid nodule is “a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma”.¹ It is a common clinical problem. Based on the method of screening, its prevalence varies from 2-6% by palpation, 19-35% by ultrasound and 8-65% by

autopsy.² The prevalence also increases with age, with spontaneous nodules occurring at a rate of 0-0.8% per year, beginning early in life and extending into the eighth decade.³ Thyroid nodule was the fifth most common diagnosis in ear nose and throat clinic at Trang Hospital (data from 2008-2010). Although only 5% of identified

nodules are malignant^{4,5} It is a challenge for clinicians to determine whether a nodule is malignant and should be surgically removed or benign and treated conservatively. With advances in diagnostic imaging technology and cytopathologic examination, trends of management of solitary thyroid nodules are changing to a more conservative approach in recent years. The aim of this study was to evaluate clinical and pathological characteristics of patients with solitary thyroid nodules in Trang Hospital and to streamline the management policy for the setting of the hospital.

Materials and methods

This study is a retrospective descriptive study. Patients with clinical diagnosis of solitary thyroid nodules and underwent thyroidectomy in Trang Hospital (either by department of ear nose and throat or department of surgery) during January 2002 through September 2010 were studied. Six hundred and eighty three medical records were reviewed, and demographic data, together with clinical, laboratory findings and cyto-histopathological features were obtained. Patients missing important data were excluded from this study (e.g. size of nodules, duration of disease, pathological result). Finally, medical records of 620 patients were used in this study.

In evaluating of thyroid function test (TFT), patients were classified into 4 groups as: no test done, hypothyroid, euthyroid and hyperthyroid. For fine needle aspiration cytology (FNAC), the results were classified into 5 categories as: benign (include nodular goiter, cyst, thyroiditis), undetermined (include follicular lesion, atypia of undetermined significance),

suspicious for malignancy, malignancy, and non-diagnostic (ND). All FNAC were alcohol-fixed preparation stained by Papanicolaou technique. Ultrasonographic (US) results were grouped into: cystic, solid and mixed or complex cyst. Pathological results were defined as benign or malignant.

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 16 software (SPSS, Chicago, IL, USA). Student's t test was used for continuous variables and chi-squared test or Fisher's exact test were used for nominal data. A p-value of 0.05 or less was deemed significant.

Results

A total of 620 patients underwent thyroidectomy during the study period. There were 50 (8%) men and 570 (92%) women, with a male to female ratio of 1:11.5. The demographic data of patients were shown in Table 1. About one-third (29.5%) of surgery performed in age group of 31-40 years. (Figure 1)

Three hundred and forty one patients (55%) had thyroid function test before treatment, most of them (304/341, 89%) were euthyroid. Three hundred and sixty one patients (58%) had FNAC results before surgery. Of these cases, 100 (27.7%) were classified as benign, 58 (16.1%) as undetermined, 17 (4.7%) as suspicious for malignancy, 17 (4.7%) as malignancy and 169 (46.8%) as ND. ND nodules on FNAC had average size of 2.8 ± 1 cm, which was not different from diagnostic nodules on FNAC that had average size of 2.7 ± 1.1 cm ($p=0.4$). Only 24 patients (3.9%) had ultrasound (US); of these, 4 were cystic, 16 were solid and 4 were mixed or complex cysts.

Table 1 Demographic data of patients (n=620)

	Number or Mean \pm S.D.
Sex	
Male	50 (8.1%) Male : Female : 1 : 11.5
Female	570 (91.9%)
Age (years)	40.54 \pm 13.05 (range 5-86)
Duration of diseases (months)	28.25 \pm 36.87 (range 1-360)
Nodule size (cm)	2.8 \pm 1.16

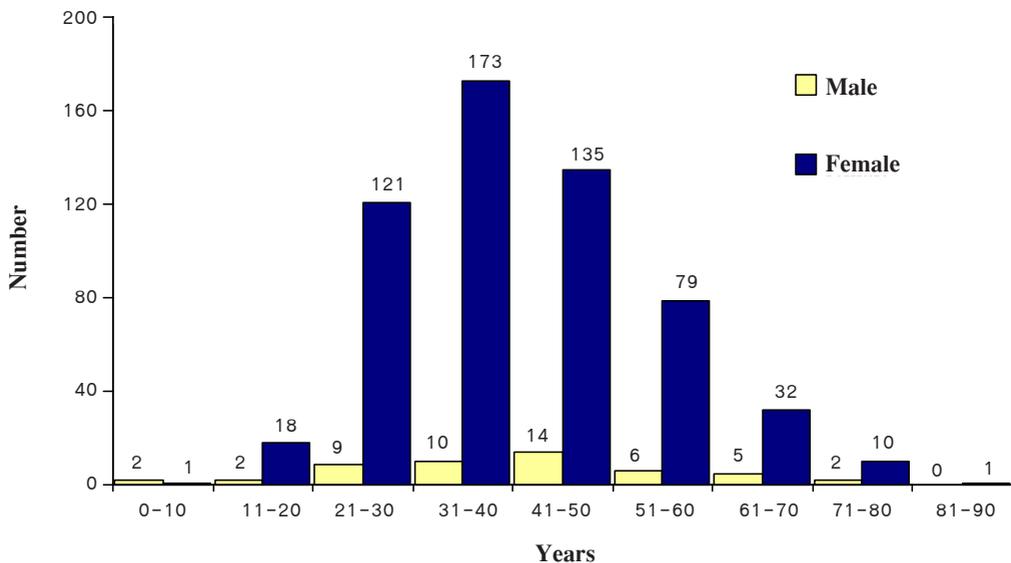


Figure 1 Age groups distribution of patients

The final pathological results were benign in 484 cases (78.1%) and malignancy in 136 cases (21.9%). In benign group (Table 2), 309 (63.8%) were nodular goiter, 55 (11.4%) were follicular adenoma, 50 (10.3%) were multinodular goiter, 25 (5.2%) were nodular goiter mixed with thyroiditis, 24 (5%) were thyroiditis and 21 (4.3%) were other diagnosis. For malignant group (Table 3),

75 (61.8%) were papillary thyroid carcinoma (PTC), 44 (32.4%) were follicular thyroid carcinoma (FTC), while 8 were other malignancy (3 medullary carcinoma, 5 Hurthle cell carcinoma). Patients with malignant disease were younger as compared to patients with benign disease, but not statistically significant (38.8 \pm 1.3 vs 41 \pm 0.6 years, p=0.08). Duration of diseases were not different between

malignant and benign group (28.3 ± 3 vs 29.1 ± 1.7 years, $p=0.3$). Rate of malignancy in men were comparable with women (24% vs 21.8%). Thirty-nine of 136 patients (28.7%) in malignant group were in age group of 21–30 years. But rate of malignancy was highest in patients of age 20 or less (9/23 or 39%) and also high in patients with age 21–30 years (39/91 or 30%). When group together, patients with age of 30 or less had significant risk of malignancy than others age group with odds ratio of 1.67 (95% CI 1.25–2.3, $p<0.001$) (Table 4).

Seven of 12 patients with hypothyroid had malignancy, the remaining 5 in this group were thyroiditis. While patients with euthyroid and hyperthyroid had malignancy 24.3% and 16% respectively. The rate of malignancy was significantly high in hypothyroid patients when

compared to patients with euthyroid or hyperthyroid (Fisher's exact, $p=0.008$). (Table 4) Patients with FNAC had the same malignant rate from pathological results as patients without FNAC (21.9% vs 22%). Of 100 patients with benign FNAC results, 87 also had benign pathological results. Sixteen of 17 patients (94.1%) with malignancy on FNAC also had malignant pathological results. Thirteen of 17 patients (74.5%) with suspicious of malignancy on FNAC had malignant pathological results. FNAC had positive predictive value for malignancy of 85.3%, and a likelihood ratio of 14.8. Twelve of 58 patients (20.7%) with undetermined on FNAC had malignant pathological results. While ND on FNAC had 14.8% (25 of 169 patients) rate of malignancy (Table 5).

Table 2 Distribution of histopathologically proved benign thyroid lesions

Pathology	Number	(%)
Nodular goiter	309	(63.8)
Follicular adenoma	55	(11.4)
Thyroiditis	24	(5)
Nodular goiter and thyroiditis	25	(5.2)
Multinodular goiter	50	(10.3)
Others		
Colloid cyst	9	(1.9)
Benign cyst	2	(0.4)
Cyst wall	2	(0.4)
Nodular hyperplasia	1	(0.2)
Diffuse hyperplasia	1	(0.2)
Other mixed lesions	6	(1.2)
Total	484	(100)

Table 3 Distribution of histopathologically proved malignant thyroid lesions

Pathology	Number	(%)
Papillary carcinoma	84	(61.8)
Follicular carcinoma	44	(32.3)
Medullar carcinoma	3	(2.2)
Hurthle cell carcinoma	5	(3.7)
Total	136	(100)

Table 4 Demographic data and clinical features of patients with solitary thyroid nodule (n=620) and were affected by either histopathological benign or malignant lesions

	Benign (± SD or %)	Malignant (± SD or %)	% of malignant	P-value
Sex				
Male	38 (6.1)	12 (2)	24.0	
Female	446 (71.9)	124 (20)	21.8	
Age (years)	41.8 (±0.6)	38.8 (±1.25)		P=0.08
Age group				
0-30 years	105 (11.9)	48 (7.7)	31.4	P<0.001*
31-70 years	370 (59.7)	84 (13.6)	18.6	
71 years or more	9 (1.5)	4 (0.6)	30.8	P=0.26**
Duration of diseases (months)	29.05 (±1.7)	25.38 (±3)	-	P=0.3
Nodule size (cm)	2.76 (±0.05)	2.92 (±0.1)	-	P=0.4
Functional status*				
Not done	228	51		
Hypothyroid	5 (1.5)	7 (2)	58.3	P=0.008***
Euthyroid	230 (67.4)	74 (21.7)	24.3	
Hyperthyroid	21 (6.2)	4 (1.2)	16.0	

*Only cases with available data were used to calculate (functional status n=381)

*Odds ratio = 1.7 (95% CI=1.25-2.3 P=0.0008)

**Odds ratio = 1.67 (95% CI=0.72-3.84 P=0.26)

***Fisher's exact test

Table 5 Fine needle aspiration cytology reports and pathologic results (n=361)

FNAC category	Benign (%)	Malignant (%)	% of malignant
Benign	87 (24.1)	13 (3.6)	13.0%
Undetermine	46 (12.8)	12 (3.3)	20.7%
Suspicious for malignancy	4 (1.1)	13 (3.6)	76.5%
Malignancy	1 (0.3)	16 (4.4)	94.1%
Nondiagnostic	144 (39.9)	25 (6.5)	14.8%

Positive predictive value for malignancy = 85.3%

Likelihood ratio for diagnostic of malignancy = 14.8

Discussion

Solitary thyroid nodules are a common clinical problem and are more common in women.^{4,6} Our study had male to female ratio of 1:11.5, comparable with previous studies.^{7,8} The prevalence of thyroid nodule increases with age,³⁻⁶ but usually present in third to fourth decades of life as shown in our study.

Most of solitary thyroid nodules are euthyroid by clinical and laboratory test. As in this study, 89% of patients who had TFT before treatment were euthyroid. But 45% of cases in our study did not have TFT (Thyroid stimulating hormone (TSH) cost 200 Thai Baht/test, Free T4 cost 200 THB/test). The reasons could be that most of patients had clinically euthyroid at time of presentation and TFT that sent before year 2006 at Trang Hospital would take few days for results. So some of clinicians shifted to other investigations or started treatment. However, TSH is recommended by American Thyroid Association as initial evaluation in management guidelines for patient with thyroid nodules

(recommendation A).¹ If TSH level is subnormal and nodule is functioning on scintigraphy, the risk of malignancy is very small and can be treated medically.¹ While patients with high TSH level, there might be cold nodule on scintigraphy and need further investigation. However, there was no case that underwent scintigraphy in our study, because scintigraphy is not available at our institute and must refer to other institute (Songklanagarind Hospital, cost 800 Thai Baht/test) if indicated with waiting time for 3 to 4 weeks. Although there were small numbers of patients with hypothyroid in our study, but 7 in 12 of them had malignant pathology that significant higher than patients with euthyroid or hyperthyroid. So patients with high TSH and cold nodule on thyroid scan, particularly when nodule is solid on ultrasound, clinicians should aware of being malignancy.⁶

The American thyroid association recommended that thyroid ultrasonography should be performed in all patients with thyroid nodule (recommendation A).¹ US is a safe, non-invasive

and effective method to know whether a nodule is solid, cystic or mixed.³ Some features of US such as solid hypoechoic nodule, microcalcification, irregular margin, increase nodular flow and evidence of regional lymphadenopathy - though not specific but are associated with risk of malignancy.³⁻⁶ US is also useful as a guide for FNAC and increases yield of FNAC especially in cases with previous ND on FNAC.^{1,3} In our hospital, cost of US (650 Thai Baht) is relatively high when compared to other investigations and the appointment usually takes 1 to 2 weeks. So only small number (24) of patients in our study had US. We intend to use US as a guide for FNAC in patients with previous ND category (Figure 2).

The prevalence of malignancy in thyroid nodule is 5%.^{4,5} Pathological reports from our study found malignant diseases in 21.9% of cases, incidence was relatively high when compare to 2 studies in Thai people.^{7,8} This might due to cases selection, because many cases in our study had FNAC before surgery, while previous studies had not. With current thyroid FNAC practice, the percentage of resected nodules that are malignant exceeds 50%.⁹ For benign group most common pathology was nodular goiter (63.8%), followed by follicular adenoma (11.4%) that not differed from previous studies.^{7,8,10,11} However, 10.3% of benign group in our study had pathological reports as multinodular goiter, shown that evaluation of nodules by palpation were unreliable. US may improve the accuracy.¹² For malignant group, differentiated thyroid carcinoma were comprised more than 90% in our study (61.8% PTC, 32.4% FTC), also the same as

previous studies.^{7,8,10,11} No case of lymphoma or anaplastic carcinoma in our study. It might be that many patients had FNAC, and if FNAC results were lymphoma or anaplastic cancer, patients had the treatment modalities other than surgery.

Age of patients was not different between benign and malignant group (41.0 ± 12.55 vs 38.8 ± 14.61 years). Risk of malignancy is high in very young (age of 20 or less) and very old (70 years of more) patients.⁵ Our study shown significant high risk of malignancy in patients with age of 30 or less. Patients in age of 21-30 years also had high risk of malignancy in our study, because we recorded age of patients at time of surgery not at time of onset, so some of patients might exactly had diseases before 20 years old. There was also high risk of malignancy in patients with age of 70 years or more from our study but not statistically significant, this might due to small number of patients (Table 4). Duration of diseases was also the same between benign and malignant group in our study ($p=0.3$). Most of thyroid cancers are differentiated cancer that run benign course, so duration of diseases cannot use for prediction of malignancy.

FNAC is accepted as the most accurate and cost effective method for evaluating thyroid nodules.^{1,3} ND-FNAC results occur in 2 to 20% of cases and occur lesser when performed with US guidance. Ideally ND categories should be limited to no more than 10% of thyroid FNAC.⁹ Forty-six point eight percent of cases with FNAC done in our study had ND results. However, the size of nodule in patients with ND-FNAC were not different from patients with diagnostic FNAC

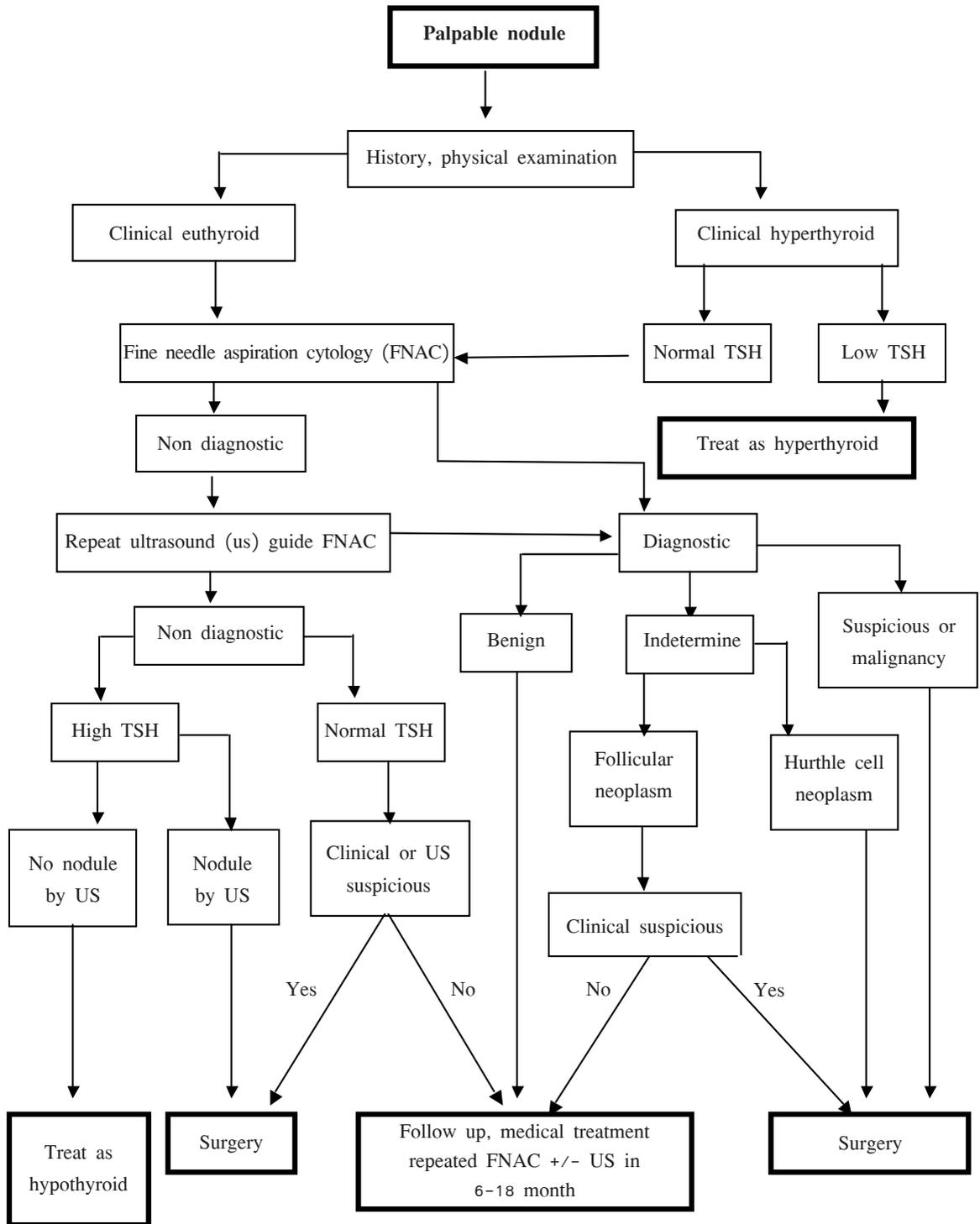


Figure 2 Algorithm for management of palpable thyroid nodules (modified from references 1,5,6)

($p=0.4$), same as previous reported by Richards et al.¹³ Experience of clinicians in FNAC might be the causes of very high rate ND-FNAC, especially in early period of this study (before year 2006). With more experiences, the rate of diagnostic FNAC was much improved in last few years of study. The sensitivity and specificity of FNAC varied from 43-98% and 72-100% respectively with overall sensitivity greater than 80% and specificity greater than 90%.^{3,13} In our study, we defined the FNAC categories closed to the Bethesda system for reporting thyroid cytopathology (TBSRTC 2007),⁹ so risk of malignancy could be compared. Results of our study had shown malignant risk of 21.7% in undetermined group, 76.5% in suspicious for malignancy and 94.1% in malignancy categories which comparable to TBSRTC. Positive predictive value was 85.3% and likelihood ratio was 14.8. However, only 58% of patients in our study had FNAC done. The efficacy of FNAC was quite reliable. In benign category, we had 13% risk of malignancy that higher than TBSRTC. This might be that interpretation as cysts were included in benign category, and cystic lesions might be mixed cysts that had malignant risk higher than purely cystic lesions. Undetermined category in our study also included cases with Hurthle cell (which FNAC cannot define whether it is adenoma or carcinoma)¹⁵ that have risk of malignancy 15 to 45%.⁹ Most of patients (80%) without FNAC performed also had benign diseases. According to FNAC and final pathologic results, many patients in this study had benign diseases that could avoid unnecessary operation and treated expectantly. The number of patients that can be treated

conservatively would be greater if all patients had FNAC in diagnostic work up. Based on these data, we finally proposed a management algorithm of solitary thyroid nodules that appropriate for our hospital setting (Figure 2).

Conclusions

Although solitary thyroid nodules are common, most of them are benign and can be treated conservatively. Very young patients or hypothyroid patients are associated with high risk of malignancy in our study. FNAC correlates well with pathologic results. We encourage use of FNAC in treatment plan for solitary thyroid nodules.

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