

## RESEARCH ARTICLE

## Accuracy of Triple Diagnostic Test in Patients with Thyroid Nodule at Dr. Cipto Mangunkusumo General Hospital

Diani Kartini, Gunawan Wibisana\*

Department of Surgery, FM Universitas Indonesia-  
Dr. Cipto Mangunkusumo General Hospital

\*Corresponding author: gunwibisana@gmail.com

Accepted 3 Maret 2017

DOI: 10.23886/ejki.5.7603.38-43

### Abstract

The aim of the study is to evaluate the accuracy of triple diagnostic test on thyroid nodules. The data from patients' medical records who came to Cipto Mangunkusumo General Hospital for the first time or for evaluation of thyroid nodule and patients who underwent thyroidectomy during 2010 to 2011. Clinical examination was scored by McGill Thyroid Nodule Score. ROC procedure was performed to obtain clinical cut-off scores of diagnosis of malignant. Ultrasonography (USG) result was considered malignant for TIRADS 4, 5, and 6. If clinical, USG and histopathology examinations of triple diagnostic give positive results, it will be classified as concordant malignant whereas if all those three show benign results, the classification is benign. Thyroid carcinoma was found in 134 out of 161 patients with thyroid nodule. There were 84 patients with concordant results for all three elements of the triple test. Out of 84 patients with concordant triple diagnostic results, there were 53 malignant cases (32.9%) and 31 benign cases (19.3%). Main histopathological findings among patients with thyroid carcinoma was papillary (90.3%), follicular (3%), medullary (0.7%), and anaplastic (6%). The sensitivity and specificity of triple diagnostic was 77% and 94%, with positive predictive value of 98%, negative predictive value of 51.6% and accuracy of 80.9%. Combination of clinical findings, USG, and FNAB gave malignant probability of 92%, better than combination of clinical findings and USG (81.6%) or clinical findings and FNAB (87%). Triple diagnostic cannot be used as an ideal test to replace frozen section examination in managing thyroid nodule. However, in cases with concordant results of each triple diagnostic's element, the positive predictive value (98%) and malignant probability (92%) is high.

**Keywords:** thyroid nodule, triple diagnostic, accuracy.

## Akurasi Metode Triple Diagnostic pada Pasien Nodul Tiroid di RSUPN Dr. Cipto Mangunkusumo

### Abstrak

Tujuan penelitian ini untuk mengevaluasi nilai diagnostik metode triple diagnostic pada nodul tiroid. Studi ini menggunakan data rekam medis pasien RSUPN dr. Cipto Mangunkusumo yang dilakukan pemeriksaan nodul tiroid dan pasien tiroidektomi tahun 2010-2011. Pemeriksaan klinis dinilai dengan McGill Thyroid Nodule Score. Prosedur ROC dilakukan untuk mendapatkan nilai klinis tolok ukur diagnosis keganasan. Hasil USG dipertimbangkan ganas untuk TIRADS 4,5, dan 6. Bila dalam temuan klinis, pemeriksaan USG, dan histopatologis triple diagnostic memberikan hasil positif maka tergolong ganas, sedangkan bila dari ketiga pemeriksaan menunjukkan hasil sesuai dengan jinak, maka tergolong jinak. Karsinoma tiroid terdapat pada 134 dari 161 pasien nodul tiroid. Terdapat 84 pasien yang menunjukkan hasil sesuai ketiga elemen triple test. Didapatkan 53 (32.9%) kasus ganas dan 31 (19.3%) kasus jinak. Temuan histopatologis pasien karsinoma tiroid berupa papiler (90.3%), anaplastik (6%), folikuler (3%), dan meduler (0.7%). Tingkat sensitivitas dan spesifisitas uji triple diagnostic 77% dan 94%, dengan nilai prediktif positif 98%, nilai prediktif negatif 51.6%, dan nilai akurasi 80.9%. Kombinasi temuan klinis, USG, dan FNAB memberikan 92% diagnosis ganas lebih baik dibandingkan kombinasi temuan klinis dan USG (81.6%) atau temuan klinis dan FNAB (87%). Triple diagnostic tidak dapat digunakan sebagai pemeriksaan ideal untuk menggantikan pemeriksaan potong beku dalam tata laksana nodul tiroid. Pada kasus yang sesuai dengan prediksi keganasan memberikan nilai prediktif positif 98% kemungkinan ganas 92% cukup tinggi.

**Kata Kunci:** nodul tiroid, triple diagnostic, akurasi.

**Introduction**

Indonesian Cancer Registration<sup>1</sup> reported that thyroid carcinoma's relative frequency is 4.43 %, ranks the ninth out of tenth most common malignancies. Thyroid carcinoma is classified as slow going tumor in the terms of growth, with low morbidity and mortality. A fraction of those cancers however, grows faster and is highly malignant with a fatal prognosis. Thyroid carcinoma mortality rate is only 0.4% of all cancer deaths, but the problem is how to recognize which thyroid gland enlargement (nodules) is malignant, because there are a lot of non-carcinoma disorders of thyroid nodules.<sup>1</sup>

In Indonesia, it is still common to perform intra-operative frozen section examination to determine whether the thyroid nodule is malignant or benign in order to decide the definitive action as well as the type of surgery to be performed. Frozen section examination has some draw backs, it is more costly, longer anesthesia time at all costs, as well as the relative lack of availability of these modality in every hospital.<sup>2</sup>

The aim of this study is to evaluate the accuracy of triple diagnostic on thyroid nodules consisting of clinical findings, USG, and fine needle aspiration biopsy (FNAB), compared to frozen section with histopathology findings as the gold standard. We expect that triple diagnostic can predict types of surgery more accurately compared to frozen section.

**Methods**

A diagnostic study was done to compare triple diagnostic method with histopathologic examination. The data used in this study were extracted from patients' medical records. The target population was patients with thyroid nodules and the inclusion criteria were patients with thyroid nodules who came to Cipto Mangunkusumo General Hospital at surgical oncology clinic for the first time or for evaluation of thyroid nodule and patients who eventually underwent thyroidectomy during 2010 to 2011. Patients with one or more metastatic lesions, indeterminate or atypical lesion in FNAB results and incomplete medical record data were excluded.

**Triple Diagnostic and Reference Standard**

Clinical examination (history and physical examination) were scored by McGill Thyroid Nodule Score/MTNs (Table 1). Diagnostic test using the receiver operating characteristic (ROC) procedure was performed to obtain clinical cut-off scores

of diagnosis of malignant. Results of the clinical examination was considered to be malignant if scores >3.

**Table 1. McGill Thyroid Nodule Score (MTNs)**

Risk factors	Score	
	1	2
Gender – male	√	
Age <20 years or >50 years	√	
History of radiation		√
Familial history of thyroid carcinoma or multiple endocrine neoplasia disease		√
Symptoms of local tumor invasion (hoarseness, dysphagia, difficulty breathing or dyspnea)		√
Rapid tumor growing without pain		√
Solitary nodule on isthmus	√	
Hard consistency		√
Regional lymph nodes enlargement		√
Diffuse margin of tumor	√	
Fixed tumor to surrounding tissue	√	

A nodule was categorized as malignant if the following signs were found during USG examination: indistinct margin of tumor, enlarged lymph nodes, in-homogenous echo structure, central microcalcification, cystic lesion with a papillary growth, hypervascularization, taller than wider shape.<sup>1</sup> Results were classified according to TIRADS USG classification (Table 2). USG result was considered malignant for TIRADS 4, 5, and 6. Cytological results of FNAB were divided into 6 categories based on Bethesda Classification (malignant, suspicious for malignancy, follicular neoplasm or suspicious for follicular neoplasm, atypic, benign, inconclusive).

If clinical, USG and histopathology examinations of triple diagnostic have positive results, it is classified as malignant concordant whereas if all those three show benign results, the classification is benign concordant.

**Table 2. Thyroid Imaging Reporting and Data System (TIRADS)**

TIRADS	Lesion	Percentage of malignancy
1	Normal	-
2	Benign	0%
3	Suspicious benign	< 5%
4a	Indeterminate	5-10%
4b	Suspicious malignant	10-80%
5	Strongly malignant	> 80%
6	Malignant	100% and confirmed by biopsy

**Statistical Analysis**

Distribution and characteristics of data from each variables were assessed using descriptive statistics and were presented in graph and tables. Inferential statistical analysis was conducted in accordance with the scale of the variables being compared, and the terms that follow the statistical calculations used.

This study used a computer program SPSS 20.0 for statistical calculations. Chi-square test were used to obtain receiver operating characteristic (ROC) curve and were performed between each element of triple diagnostic test to the gold standard (histopathology result). Multivariate analysis using logistic regression test was done in order to reveal the diagnostic value of the triple diagnostic test. In the analysis of this diagnostic test, each variable was divided into 2 groups: malignant and benign. Patients with suspected malignancy were grouped into the malignant group.

**Results**

During 2010-2011, there were 161 cases eligible for this study. Of these, 51 patients had inconclusive results or atypical cells from FNAB. Most of the thyroid nodule cases occurred in females. As many as 141 patients (87.5%) were females with a median value of 46 years old (range 10-67 years). All patients, presented with a lump on the front side of the neck.

**Table 3. Characteristics of the Subjects**

Characteristics	Total (%)
Gender	
Male	20 (12.5)
Female	141 (87.5)
Median Age (years)	46 (10-67)
Age Group (%)	
< 20 year	5 (3.1)
21 - 30 year	8 (5)
31- 40 year	36 (22.4)
41 – 50 year	60 (37.3)
51 – 60 year	35 (21.7)
>60 year	17 (10.6)
Tumor size	
≤ 4 cm	45 (28)
>4 cm	116 (72)
Histopathology	
Papillary	121 (90.3)
Follicular	4 (3)
Medullary	1 (0.7)
Anaplastic	8 (6)
Surgery	
Primary	140 (87)
Secondary	21 (13)

Malignant tissues were found in 134 out of 161 patients. The histopathology types were: papillary type 121 cases (90.3%), follicular 4 cases (3%), medullary 1 case (0.7%) and anaplastic 8 cases (6%). There were 13 patients that present distant metastases. The metastases were found in the lung (5 patients), vertebrae (3 patients), costae (3 patients), the frontal bone (1 patient) and the parietal bone (1 patient). Based on clinical examination, 81 patients classified malignant were proved in histopathology as thyroid carcinoma (Table 3). Compared to histopathology findings, this examination yielded a sensitivity of 60.4%, specificity of 77.8%, and accuracy of 63.3%. The most frequent variable in this examination were risk factors (29.8%) and hard consistency (23.1%).

**Table 4. Triple Diagnostic and Histopathological Results**

Diagnostic Methods	Histopathological		Total
	Malignant	Benign	
Clinical exam			
Malignant	81	6	87
Benign	53	21	74
USG			
Malignant	95	10	105
Benign	39	17	56
FNAB			
Malignant	78	3	81
Benign	56	24	80
Triple diagnosis			
Malignant	52	1	53
Benign	15	16	31

In USG examination, signs of malignancy were found in 95 patients (Table 3). USG sensitivity was 70.9%, specificity was 63%, and accuracy was 69,6%. Measurements of the diagnostic value for clinical examination and USG were also done using RO. Area under the curve (AUC) value of clinical and USG was 81.6%, which is greater than the diagnostic value of clinical examination alone (73.5%). There was an additional diagnostic value of 8.1% by adding USG examination. FNAB procedure showed 78 patients with malignant nodules (Table 3) produced sensitivity of 58.25%, specificity of 88.9%, and accuracy of 63.4%.

From the data above, bivariate analysis were performed (Table 4). The results showed p<0.05 in three variables: symptoms of local tumor invasion, rapid tumor growing, and hard consistency. These variables added with tumor mobility were performed multivariate analysis with p>0.05, respectively.

**Table 5. Chi-square Results Between Clinical Variables with Histopathological Findings**

Variable	p	OR (Min-Max)
Gender	0.619	0.74 (0.22-2.45)
Age	0.524	1.38 (0.51-3.71)
Family history	0.585	0.73 (0.24-2.23)
Local tumor invasion	0.014	8.77 (1.14-6.75)
Period of rapid expansion	0.013	3.96 (1.27-12.39)
Tumor consistency	< 0.001	1.4 (1.23-1.59)
Solitary nodule	0.520	0.46 (0.4-5.25)
Lymph node enlargement	0.197	2.64 (0.58-12.08)
Tumor margin	0.299	2.89 (0.36-23.24)
Tumor mobility	0.05	1.29 (1.18-1.43)

In measurements of the diagnostic value for clinical examination and FNAB, AUC value was 87% while the AUC value of clinical patients with concordant triple diagnostic results, there were 53 malignant cases (32.9%) and 31 benign cases (19.3%), while non concordant results were found in 77 cases. In patients with concordant triple diagnostic results, the overall sensitivity was 77%, specificity was 94%, positive predictive value was 98%, and negative predictive value was 51.6%, with accuracy of 80.9%. The accuracy value was lower than expected in this study. The accuracy value is strongly affected by its elements, so in order to increase the overall accuracy value we need uniformity and accuracy enhancement from all three diagnostic elements' studies. Moreover, the examination alone was 73.5%. Addition of FNAB to this combination increased the diagnostic value by 14.5%.

There were 84 patients with concordant results for all three elements of the triple test (Table 3). Based on the analysis, out of 84 data was collected retrospectively from medical records, and the diagnostic studies were not done previously, making the study susceptible to bias in data collection. Diagnostic value of triple diagnostic were measured with ROC, AUC of 92% showed better result than either combination clinical examination and USG or clinical examination and FNAB (Table 7).

**Table 6. AUC Values of Several Diagnostic Models**

Diagnostic Model	AUC Value
Clinical exam (history taking + physical exam)	73.5%
Clinical exam + USG	81.6%
Clinical exam + FNAB	87%
Triple diagnostic	92%

Frozen section was performed in 112 out of 161 patients who underwent thyroidectomy procedure, intraoperatively (Table 8). The diagnostic values were as follows; sensitivity of 65.5%, specificity of 86.3%, accuracy of 70%, positive predictive value and negative predictive value of 95.1% and 38%, respectively.

**Table 7. Frozen Section and Histopathology Results**

Frozen Section	Histopathological		Total
	Malignant	Benign	
Malignant	59	3	62
Benign	31	19	50
Total	67	17	84

**Table 8. Diagnostic Value Comparison of Triple Diagnostic and Frozen Section**

Diagnostic Value	Triple diagnostic	Frozen Section
Accuracy	80.9%	70%
Sensitivity	77%	65.5%
Specificity	94%	86.3%
PPV	98%	95.1%
NPV	51.6%	38%

**Discussion**

From 161 patients with thyroid nodules, 134 patients (83%) were presented with malignant thyroid tissue in histopathology. Papillary carcinoma is the most common type. Based on age, thyroid carcinoma distribution have the tendency to rise quietly from the 3<sup>rd</sup>-5<sup>th</sup> decade of life and go down at the 6<sup>th</sup> decade of life. This result is in accordance with other studies which stated that the tendency of thyroid nodule to appear peaked at the 4<sup>th</sup> decade and decrease at the 5<sup>th</sup> decade.<sup>1-3</sup>

We found that the majority of thyroid enlargement events occurred in female patients (87.5%). It is similar with other studies which stated that the gender distribution of the disease in Indonesia (female:male were 2:1 to 3:1).<sup>1-3</sup> From clinical examination, low value of diagnostic results, especially specificity (77.8%), could be caused by the method of data collection which were conducted retrospectively from medical records and technical variation among physicians who performed the examinations. In addition, sometimes the typical signs of thyroid carcinoma were not found during clinical examination, except in occurrence of infiltration into the surrounding tissue and lymph

node enlargement.<sup>4</sup> The clinical malignancy scoring system by using MTNs is more appropriate to use in non-retrospective study. From bivariate test, clinical factor ( $p < 0.05$ ) presented statistically significance results. This means that we should do a thorough clinical examination in order to collect accurate signs and symptoms of thyroid carcinoma.

Triple diagnostic is difficult to conduct in thyroid carcinoma because most patients do not present with typical signs and symptoms; some even present with no symptoms. It is also seen from the number of concordant results in triple diagnostic, which only 84 subjects (Table 6) or half of total subjects in this study. Among each element of triple diagnostic therapy, FNAB provided the biggest contribution in increasing the diagnostic accuracy of triple diagnostic method (Table 8). FNAB increased the AUC value of 14% from clinical examination while USG only 8.1%. When the three elements were combined together, it increased the value up to 92%. Therefore, we continue the analysis of FNAB. In this report, showed different results with other research, particularly in terms of sensitivity (58.25%) and accuracy (63.4%). The reported sensitivity of FNAB is between 80% and 95%, and accuracy ranges from 92-95%.<sup>12</sup> Currently, techniques of specimen collection with USG guided had been developed outside Indonesia, resulting in improved diagnostic values of FNAB examinations.<sup>7-9</sup> Specimen collection technique in, however, was still done with conventional ways.

In this study, frozen section did not reach the ideal as defined by the association of directors of anatomic and surgical pathology. Ideally, frozen section should not give an error rate more than 3%.<sup>10</sup> In this study, however, the false negative rate was 27,6%. So, if there is a risk or suspicion of malignancy, one should consider to continue surgical treatment even if the frozen section result is benign. This modality also has the same limitations as FNAB in determining follicular adenoma to follicular carcinoma because of inability to provide information about vascular or capsular invasion.<sup>3</sup>

Triple diagnostic reported better diagnostic value compared to frozen section however, the false negative ratio of triple diagnostic was still high (48.4%). This might be due to the limited number of subject in this study. Further research need to be done with more subjects. Treatment of thyroid nodules have been changing a lot owing to the development of numerous new diagnostic tools. When the investigation is done in combination (triple diagnostic), the accuracy will increase up to 90%.<sup>4,5</sup>

Triple diagnostic still cannot be used as an ideal test to replace frozen section examination as the basis for definitive therapy in patients with thyroid nodules. However, concordant patients with malignancy in triple diagnostic's elements showed high positive predictive value of 98%. It means that if the diagnostic test (triple diagnostic) was positive, the probability to have thyroid carcinoma would be 98%. This is supported with study by Damanik<sup>11</sup> which showed a positive predictive value of 95.1% for triple diagnostic test.

## Conclusions

Triple diagnostic for thyroid nodules still cannot be used as an ideal test to replace frozen section or histopathological result (gold standard). However, cases with concordant results of each triple diagnostic's element have high positive predictive value (98%) and malignant probability (92%). In those cases, it is still possible to perform definitive operation with the consideration of center-specific sensitivity and specificity of all triple diagnostic elements. In order to validate these results, other prospective longitudinal studies should be done with larger sample size and better data sampling method in order to avoid bias and reduce confounding factors. Moreover, diagnostic values in further studies such as intraoperative examination of thyroid sections might be explored for better diagnosis.

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