International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 5 | Issue: 3 | May – Jun 2024 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v5i3.17

Diagnostic Accuracy of Clinical Examination, Ultrasonography, and Fine-Needle Aspiration Biopsy to Determine Thyroid Nodules Malignancies

Made Gian Indra Rahayuda[1*], I Wayan Sudarsa[2], Ida Bagus Made Suryawisesa[2], I Wayan Periadijaya[3], Putu Anda Tusta Adiputra[2], and I Wayan Niryana[4]

[1]Department of General Surgery, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Denpasar, Indonesia (80113)

[2]Division of Oncology Surgery, Department of Surgery, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Denpasar, Indonesia (80113)

[3]Division of Traumatic Surgery, Department of Surgery, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah Generah Hospital, Denpasar, Indonesia (80113)

[4]Division of Neurosurgery, Department of Surgery, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Denpasar, Indonesia (80113)

E-mail: gianindrab@gmail.com; sudarsa1510@yahoo.com; gusdeck2001@yahoo.com; wayanperiadijaya@gmail.com; andatusta@yahoo.co.id; niryanawayan@gmail.com

*Correspondent author details: Made Gian Indra Rahayuda; gianindrab@gmail.com

ABSTRACT

Background: Thyroid nodules are one of the most common health problems in the thyroid gland. The increase in the number of new cancers by experts is estimated to be related to the increase in the intensity of diagnostic tests that can be performed in determining the presence of malignancy from clinical examination, ultrasound, and FNAB. ***Aim:*** Knowing the diagnostic accuracy of clinical examination, ultrasound examination, and FNAB in determining thyroid malignancy. ***Method:*** a cross-sectional study of diagnostic tests performed at Central General Hospital Prof. Dr. IGNG Ngoerah, Denpasar. The study subjects were patients with thyroid nodule abnormalities who came to the surgical oncology polyclinic. Data analysis includes descriptive statistics, bivariate analysis with Chi-Square, binary logistic regression analysis, and sensitivity and specificity test with receiver operating characteristic (ROC) curve. ***Results:*** There were 71 research subjects, 16 males (22.5%) and 55 females (77.5%) with an average age of 43.75 ± 12.52 years. The results of bivariate analysis of diagnostic accuracy showed that the number of nodules was not statistically significant with p=0.531, sensitivity 62.9%, specificity 44.4%, PPV 52.4%, and NPV 55.2%. Nodule size was not significant with p=0.286, sensitivity 45.7%, specificity 66.7%, PPV 57.1% and NPV 55.8%.the lymph nodes with a p=0.005 sensitivity of 74.3%, specificity of 58.3%, PPV of 63.4%, and NPV of 70%. Ultrasound examination (TRIADS ACR) had a p=0.003, sensitivity of 91.4%, specificity of 38.9%, PPV of 59.3%, and NPV of 82.4%, FNAB examination (Bethesda) with a p=0.005 sensitivity of 31.4%, specificity of 94.4%, PPV of 84.6%%, and NPV of 58.6%; age, gender, nodule size, and nodule number were not statistically significant. The assessment score for LNs enlargement was 4, the ultrasound score was five, and the FNAB score was 5. The ROC curve analysis obtained a sensitivity value of 77.1% and a specificity of 75% with a cut-off value of 7. A score ≥7 has a high risk of 10.13 times showing postoperative anatomical pathology with the results of malignancy p < 0.001 (95% CI 3.39-30.16), 77.1% sensitivity, 75% specificity, 75% PPV, and 77.1% NPV. ***Conclusion:*** Lymph nodes (LNs) enlargement, ultrasound score based on TIRADS ACR, and fine-needle aspiration biopsy based on Bethesda score have good enough diagnostic accuracy in determining malignancy in thyroid nodules. Meanwhile the number of nodules and nodule size did not have a significant effect on the malignancy of thyroid nodules.

Keywords: FNAB; malignancy; thyroid nodule; lymph node enlargement; ultrasound

INTRODUCTION

Thyroid nodules are one of the most common health problems in the thyroid gland. In most cases, they are harmless and not caused by any serious illness. However, when the lump begins to enlarge or interferes with the function of the thyroid or surrounding organs thyroid nodules can cause a number of complaints, one of which is thyroid cancer.

Thyroid cancer is a malignancy that occurs in the thyroid gland. In recent years, the incidence of thyroid cancer has increased rapidly worldwide.

Proliferation of tumor cells in thyroid cancer can result in the formation of nodules in the thyroid organ. Of all benign nodules on ultrasound and cytological examination, only 0.3% develop into malignant. The mechanism of thyroid nodules becoming thyroid cancer can be caused by *point* mutations or *chromosomal rearrangements [1]*. Aggressive tumor cells can metastasize to lymph nodes through local invasion and to other organs such as lung, bone, and brain hematogenically, and are a predictor of mortality in patients [2].

The incidence of thyroid cancer has increased significantly since the mid-1990s, with an estimated incidence in the United States of 53,990 cases in 2018. It is the most common malignancy among endocrine gland cancers and represents approximately 3% of all malignant tumors in humans. 75% of cases occur in women and two-thirds of cases occur in people under 55 years old. The mortality rate from thyroid cancer has remained stable in women, but has increased by about 1% per year since 1983 in men and resulted in approximately 2,060 deaths in 2018. Despite the low mortality rate, about 20% of patients experience local recurrence, and distant metastasis occurs in about 10% of patients 10 years post-diagnosis [3]. Data in Bali from 2016-2021, there were 198 subjects with single thyroid nodules who underwent surgery at Sanglah General Hospital, 98 subjects were histopathologically proven cancer (follicular, papillary) after surgery [4].

This increase in the number of new cancers is thought by experts to be related to an increase in the intensity of diagnostic examinations, namely the use of high-resolution ultrasound. Other experts believe that the actual increase may also be due to environmental and lifestyle changes. The use of ultrasonography for the evaluation of thyroid disease and non-thyroid neck disease has increased the prevalence of thyroid gland nodules. Epidemiologic studies show the prevalence of thyroid nodules palpable by physical examination to be about 4-7% in women and 1% in men living in areas with sufficient iodine. With high-resolution ultrasound examination of the neck and thyroid thyroid nodules are detected in about 19% to 68% in randomly selected people, with a higher frequency appearing in women and the elderly. The clinical importance of this thyroid nodule examination lies in the need to exclude the diagnosis of thyroid cancer [3].

The thyroid gland is a relatively rare organ with malignancy, of all incidentally detected thyroid nodules, nearly 90% are benign and can be managed conservatively [5]. Only a small proportion of nodules are malignant and require surgical resection in between 7-15% of cases, depending on age, gender, history of radiation exposure, family history, among other factors [3,5]. Currently, fine needle aspiration biopsy (FNAB) is the most effective and reliable test to determine whether a nodule is malignant and requires surgery, but 10% to 40% of all samples give indeterminate results (Wei). In recent years, with the rapid development of molecular biology, various mutations and molecular regulatory and immunohistochemical markers have emerged. Among these, is the BRAF V600E mutation, which is a highly specific molecular marker for papillary thyroid carcinoma. However, this test is of dubious diagnostic value due to its low sensitivity [5,6]. All these detection methods have limitations and make it difficult to distinguish between benign and malignant tumors.

Thyroid cancer detection studies have been conducted, but there are varying results among different studies. According to a study by AACE/AME, epidemiologic factors associated with an increased risk of thyroid malignancy include a previous history of head or neck radiation especially in childhood, age less than 20 or more than 70 years, and in some studies an increased risk in males [7]. From a study by Dean et al, a different statement was obtained where the risk of thyroid nodules was higher with increasing age, female gender, iron deficiency and a history of thyroid radiation. Thyroid nodules are approximately 4 times more common in women than men [8]. Meanwhile, according to Rahimi et al, in most studies, age and gender are not associated with malignancy [9]

In terms of clinical examination, clinical predictors of thyroid malignancy include nodules of firm consistency, fixed to surrounding anatomy, presence of lymphadenopathy, and lower level predictors which include symptoms of hoarseness and/or dysphagia. The rapid growth rate observed on serial ultrasonography has also been suggested to predict malignancy, but until now its definition has been unclear [7].

In a study by Ugurlu et al, single nodules, irregular edges, and microcalcifications increased the chances of malignancy 3.6; 5.4; and 39-fold, respectively [10]. In a study by Taneri et al in 2005, multiple nodules were associated with malignancy, while in a study by Ugurlu et al in 2008, having one or two nodules increased the likelihood of malignancy [9]

In a study by McCoy et al, it was found that FNAB results in the indeterminate category were associated with histologically confirmed malignancy in 33% of patients. Of these malignant nodules, cancer grade was examined based on nodule size where malignancy was found in 24% of patients with nodules measuring 4-5.9 cm and 57% of patients with thyroid nodules measuring 8-10 cm. However, the sample size was not sufficient to show a statistically significant association. Banks et al. examined 639 patients with indeterminate FNAB results or suspicious results and found that nodules measuring 2.5 cm had the lowest probability of malignancy, with the probability of malignancy increasing by 39% with each 1 cm increase in size [7].

Based on the results of this study, thyroid nodule size should not be used as a criterion for malignancy and

thyroid nodules of any size should be suspected of being malignant [9].

High-frequency ultrasound has been the first detection modality in thyroid nodules, however ultrasound findings of benign and malignant nodules partially overlap and are highly operator-dependent. In addition, different guidelines have been proposed to classify benign and malignant thyroid nodules by conventional ultrasound examination, such as the Kwak TI-RADS, classification guidelines by the American Thyroid Association (ATA), Korean Thyroid Association/Korean Society of Thyroid Radiology (KTA/KSThR), and most recently in 2017 the American Society of Radiology (ACR) presented an updated version of TI-RADS based on large-scale clinical and evidence-based validation [11]. In Aryanti's research (2022), it was found that the combination of ultrasound characteristics, age and physical examination was able to accurately predict thyroid cancer [12].

Some studies have discrepancies and limitations which is one of the reasons it is still difficult to confirm malignant nodules. Due to the uncertainty of diagnosis, many patients experience unnecessary interventions and excessive medical treatment. Accurately distinguishing between benign and malignant nodules is important in order to provide appropriate therapy to patients. Therefore, new strategies are urgently needed to differentiate thyroid malignancy from thyroid nodules. Because of the above, the researcher is interested in conducting a diagnostic test study to determine the diagnostic accuracy of clinical factors, application of ultrasound examination, FNAB in determining thyroid malignancy.

METHODS

This study is a cross-sectional study of diagnostic tests to determine the validity of clinical factors, ultrasound examination, and FNAB in detecting thyroid malignancy. The target population in this study were oncology patients who visited Prof. Dr. I.G.N.G Ngoerah Hospital from January 1, 2016 to October 31, 2022, while the target population in this study were patients who had data on cervical ultrasound examination, thyroid FNAB, and clinical symptom monitoring.

Inclusion criteria included: 1) Patients with thyroid nodule disorders who came to the oncology surgery polyclinic; 2) Cervical ultrasound and FNAB examination of thyroid nodules have been performed; 3) Thyroid surgery and PA examination have been performed; 4) Pathological anatomy results of thyroid surgery show the results of papillary thyroid carcinoma, and follicular thyroid carcinoma; 5) Registered as a patient at Prof. Dr. I.G.N.G Ngoerah Hospital, Denpasar. Exclusion criteria included: 1) The results of anatomical pathology of thyroid surgery showed results other than papillary thyroid carcinoma, and follicular thyroid carcinoma; 2) Goitre patients; 3) Primary hypothyroidism patients; 4) Primary hyperthyroidism patients; 5) Grave's disease patients.

We collected secondary data from the medical records of patients with thyroid nodules from January 2015 to August 2022, by taking TIRADS score data from thyroid ultrasound examination results, Bethesda system scores from FNAB results, and clinical factor data through medical records of patients with thyroid nodules and thyroid carcinoma who have been diagnosed through histopathological examination in the Anatomical Pathology section of Prof. Dr. I.G.N.G Ngoerah Hospital. Then, researchers set aside medical records that had exclusion criteria.

Researchers collected 43 samples of medical records of thyroid tumor patients who underwent ultrasound, FNAB, and clinical examinations and then matched them with the gold standard, namely the results of histopathological examination / anatomical pathology biopsy of thyroid surgery. Data analysis was carried out with the help of Stastical Package for the Social Sciences (SPSS) which included descriptive statistical analysis , bivariate analysis, and binary logistic regression analysis.

RESULTS

This study was conducted from May 2021 to November 2022. This study involved 71 patients with thyroid nodules who met the inclusion criteria. The basic characteristics of the study subjects can be seen in Table 1. If the data distribution value is not significant, the number written in the table is the median value. On the other hand, if the data distribution value is normal, the table contains the mean value according to the variable analysis.

Of the 71 research subjects, consisting of 16 men (22.5%) and 55 women (77.5%) with an average age of 43.75 ± 12.52 years. The distribution of age group data was dominated by people with an age range of < 40 years by 23 people (32.4%) and ≥ 40 years by 48 people (67.6%).

TABLE 1: Characteristic features of study subjects (n=71).

Characteristics	frequency (%)
Age (years) Mean ± SD	43,75 ± 12,52
< 40 years	23 (32,4)
≥ 40 years	48 (67,6)
Gender, n (%)	
Male	16 (22,5)
Female	55 (77,5)
Number of nodules	
SNT	29 (40,8)
MNT	42 (59,2)
Nodule Size [median (minimum-maximum) cm]	***4 (1-13)***
< 5 cm	43 (60,6)
≥ 5 cm	28 (39,4)
Enlarged Lymph nodes (LNs)	
Yes	41 (57,7)
No	30 (42,3)
Ultrasound examination results based on TIRADS ACR categories	
Benign (Grades 1-3)	17 (23,9)
TR 1	2 (2,8)
TR 2	4 (5,6)
TR 3	11 (15,5)
Ferocious (Grades 4-5)	54 (76,1)
TR 4	33 (46,5)
TR 5	21 (29,6)
FNAB examination results based on Bethesda category	
Benign (Grades 1-4)	58 (81.6)
Bethesda 1	2 (2,8)
Bethesda 2	29 (40,8)
Bethesda 3	1 (1,4)
Bethesda 4	26 (36,6)
Ganas (Grades 5-6)	13 (18,3)
Bethesda 5	13 (18,3)
Bethesda 6	0 (0)
Postoperative anatomic pathology biopsy features	
Benign	36 (50,7)
Malignant	35 (49,3)
Papillary Thyroid Carcinoma	34 (47,8)
Follicular Thyroid Carcinoma	1 (1,4)

FNAB = fine-needle aspiration biopsy; TIRADS ACR = Thyroid Imaging Reporting and Data System of American Society of Radiology; ultrasound = ultrasonography.

The presence of nodules in all samples was classified into the number of nodules, size of nodules, and presence or absence of enlarged lymph nodes. Most people were recorded as having multiple nodules (MNT), as many as 42 people (59.2%), while the remaining 29 people had a history of SNT (40.8%). Nodule size with a median of 4 cm with a range of 1-13 cm was found to be below 5 cm (43 people 60.6%) and ≥5 cm (28 people 39.4%). Lymph node enlargement in 41 (57.7%) people and the rest did not show such enlargement (42.3%).

The results of ultrasound assessment based on TIRADS ACR grade 1-3 17 (23.9%) and TIRADS ACR grade 4-5 54 (76.1%). FNAB examination based on the Bethesda category were benign (grades 1-4) as many as 58 people (77.5%) and malignant (grades 5-6) as many as 13 people (22.5%).

The postoperative anatomical pathology biopsy results clearly showed that the benign category (50.7%) was experienced by 36 people, while the malignant category included the remaining 35 people (49.3%). The existence of different percentages between ultrasound, FNAB, and anatomical pathology biopsy diagnostic tools needs to be further studied through a series of diagnostic tests.

In this study, to determine the significance of the relationship of clinical examination, ultrasonography and fine-needle aspiration biopsy to the results of anatomical pathology and see the risk, the Chi-Square test was performed, the significant value with $p < 0.05$. Data are presented in Table 2.

The results of Chi-Square analysis showed that there was no significant difference between age, gender,

number of nodules and nodule size with postoperative anatomical pathology results. Lymph node enlargement has a significant difference with the result of p 0.005 and obtained OR 4.04 (CI95% 1.47-11.06) which means that enlarged LNs have a risk of malignancy according to the results of postoperative anatomical pathology by 4x.

TABLE 2: Chi-Square test between age, gender, clinical examination, ultrasonography and fine-needle aspiration biopsy on anatomic pathology results.

Variables	Postoperative anatomic pathology biopsy features		OR	95% CI	P-value
	Malignant n 35 (%)	Benign n 36 (%)			
Age					
< 40 years	13 (37,1)	10 (27,8)	1,54	0,56-4,18	0,399
≥ 40 years	22 (62,9)	26 (72,2)			
Gender					
Male	7 (20,0)	9 (25,0)	0,75	0,245-2,29	0,614
Female	28 (80,0)	27 (75,0)			
Number of nodules					
MNT	22 (62,9)	20 (55,6)	1,35	0,52-3,50	0,531
SNT	13 (37,1)	16 (44,4)			
Nodule Size					
≥ 5 cm	16 (45,7)	12 (33,3)	1,68	0,64-4,40	0,286
< 5 cm	19 (54,3)	24 (66,7)			
Enlargement of LNs					
Yes	26 (74,2)	15 (41,7)	4,04	1,47-11,06	0,005*
No	9 (25,8)	21 (58,3)			
USG (TIRADS ACR)					
Ferocious (Grades 4-5)	32 (91,4)	22 (61,1)	6,78	1,74-24,45	0,003*
Benign (Grades 1-3)	3 (8,6)	14 (38,9)			
FNAB (Bethesda)					
Ganas (Grades 5-6)	11 (31,4)	2 (5,6)	7,79	1,58-38,38	0,005*
Benign (Grades 1-4)	24 (68,6)	34 (94,4)			

*Significant p<0.05.

The results of ultrasound examination based on the division of TIRADS ACR were also found to be statistically significant with a p result of 0.003 and an OR of 6.78 (95% CI1.74-24.45), which means that the results of ultrasound examination based on TIRADS ACR have a risk of malignancy according to the results of postoperative anatomical pathology by 6.8x.

The results of the FNAB examination based on the division of Bethesda were also found to be statistically significant with a p result of 0.005 and an OR of 7.79 (95% CI 1.58-38.38), which means that the results of the FNAB examination based on Bethesda have a risk of malignancy according to the results of postoperative anatomical pathology by 7.8 times. Diagnostic test results were used to assess the sensitivity, specificity, positive predictive value and negative predictive value of clinical examination in determining thyroid malignancy at Prof. Dr. I.G.N.G Ngoerah Hospital. The analysis used was Chi Square-presetage. The data of this test is presented in Table 3.

The results obtained in Table 3 that the number of nodules and nodule size are not statistically significant, for LNs enlargement, it is found to be meaningful with the results of p 0.005, sensitivity 74.3%, specificity 58.3%, PPV value 63.4% and NPV 70.0. Ultrasound results were found statistically significant with p 0.003, sensitivity 91.4%, specificity 38.9%, PPV 59.3% and NPV 82.4%. FNAB results obtained sensitivity 31.4%, specificity 94.4%, PPV 84.6% and NPV 58.6%. From the overall data obtained, it can be concluded that LNs enlargement has sufficient sensitivity, and the value of specificity, PPV, and NPV is low, while for ultrasound the sensitivity is very good, low specificity, sufficient PPV and low NPV, for FNAB the sensitivity is less, the specificity is very good with good PPV and sufficient NPV, From these results, the overall data for LNs, ultrasound and FNAB enlargement does not have the best data so this study will combine the three data to get good results in sensitivity, specificity, PPV and NPV to be better and can be applied as a basis for consideration of further thyroid nodule therapy.

TABLE 3: Diagnostic test results of clinical examination, ultrasonography and fine-needle aspiration biopsy against anatomic pathology biopsy results.

Variables	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	P - value
Clinical examination					
Number of nodules	62,9	44,4	52,4	55,2	0,531
Nodule Size	45,7	66,7	57,1	55,8	0,286
Enlargement of LNs	74,3	58,3	63,4	70,0	0,005*
USG (TIRADS ACR)	91,4	38,9	59,3	82,4	0,003*
FNAB (Bethesda)	31,4	94,4	84,6	58,6	0,005*

In this study, the multivariate analysis used was binary logistic regression analysis, to calculate the regression coefficient of the diagnostic parameters for the category of clinical factors, ultrasound examination results and FNAB results. The results of the analysis are presented in Table 4.

TABLE 4: Multiple Logistic Regression Test of clinical examination, ultrasonography and fine-needle aspiration biopsy on anatomical pathology biopsy results.

Variables	Adjusted Odds Ratio	95% CI	P-value
Tumor size	0,853	0,262	0,791
Number of nodules	1,075	0,328	0,904
Enlargement of LNs	**3,662**	**1,157**	**0,027**
USG (TIRADS ACR)	**5,079**	**1,148**	**0,032**
FNAB (Bethesda)	**4,742**	**0,815**	**0,083**

The results in this study obtained significant parameter coefficients with p<0.25 were magnifying LNs, USD and FNAB with the score used according to the Adjusted Odds Ratio.

The weight of the assessment score for LNs enlargement is 4, the assessment score for ultrasound is 5 and the assessment score based on FNAB is 5.

TABLE 5: Score value of LNs enlargement, ultrasonography and fine-needle aspiration biopsy on thyroid nodule malignancy.

Variables	Score
Enlargement of LNs	4
USG (TIRADS ACR)	5
FNAB (Bethesda)	5

The results of the score obtained based on the value of the logistic regression analysis, namely the sum of the LNs, ultrasound and FNAB enlargement scores, then determined the score limit associated with the malignancy threshold results according to the results of postoperative anatomical pathology using the statistical method Receiver Operating Characteristic (ROC) procedure and assessing the Area Under the Curve (AUC). The ROC curve results are presented in Figure 1 with the significance results in Table 6.

TABLE 6: Sensitivity, specificity and cut off points of malignancy in thyroid nodules.

Variables	AUC	95% CI	Sensitivity	Specificity	Cut-off points	p
LNs magnification, ultrasound, and FNAB	0,792	0,686 - 0,899	77,1%	75%	7	<0,001

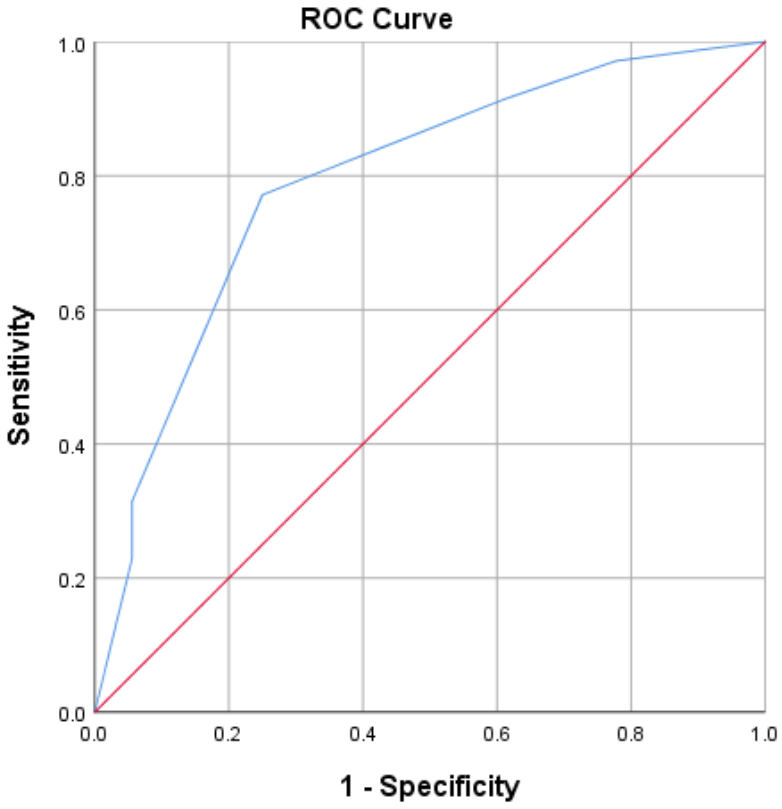

FIGURE 1: Receiver Operating Characteristic Curve.

The results of the ROC curve analysis obtained a sensitivity value of 77.1% and specificity of 75% with a cut off value of 7.

Furthermore, based on these values, a risk model for malignancy in thyroid nodules is compiled which is presented in Table 7.

TABLE 7: The relationship of the combined value of LNs, ultrasound, and FNAB enlargement with a cutoff of 7 to postoperative anatomic pathology biopsy features.

Variables	Postoperative anatomic pathology biopsy features		OR	95% CI	P-value
	Malignant n 35 (%)	Benign n 36 (%)			
LNs magnification, ultrasound, and FNAB					
Score ≥7 (high risk)	27 (77,1)	9 (25,0)	10,13	3,39-30,16	<0,001
Score <7 (low risk)	8 (22,9)	27 (75,0)			

TABLE 8: Accuracy of combined examination of lymph node enlargement, ultrasonography and fine-needle aspiration biopsy for malignancy in thyroid nodules.

Variables	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	P - value
Accuracy of combined LNs, ultrasound, and FNAB magnification	77.1	75,0	75,0	55,8	<0,001

In this study, it was concluded that enlarged LNs, ultrasound, and FNAB with a score value ≥7 had a high risk of 10.13 times showing a postoperative anatomical pathology picture with malignancy results compared to a score value <7 (low risk), significant p < 0.001 (95% CI 3.39-30.16).

The accuracy of lymph node enlargement examination, ultrasonography and fine-needle aspiration biopsy on thyroid nodule malignancy is statistically significant with the results of p < 0.001, sensitivity of 77.1% specificity of 75%, positive predictive value of 75% and negative prediction of 55.8%.

DISCUSSION

In this study, the mean age of the study subjects was 43.75 ± 12.52 years. The distribution of age group data was dominated by people with an age range of < 40 years by 23 people (32.4%) and ≥ 40 years by 48 people (67.6%). The results of this study are the same as those conducted by [13] in 100 subjects with thyroid nodules with a mean age of 43.7 ± 11.5 (range 22-60) years. Thyroid cancer can occur in all age groups, but more in adults aged 45 to 54 years, with an average age of 50 years at diagnosis (NCI, 2015). Hughes (2011) also states that the incidence of thyroid cancer increases during the fourth and fifth decades of life [14]. In contrast to the NCCN, (2014) which found that young age is common for thyroid cancer. Across the literature, age onset appears as a bell-shaped curve, with the highest incidence in the second, third and fourth decades of life. The increase in diagnosis may be due to accidental tumor findings on imaging studies [15]. The results of Aryanti's research (2022) show that age and consistency of physical examination provide a predictive value in thyroid cancer of 30% [12]. However, in this study, the results of Chi-Square analysis found that there was no significant difference between age and postoperative anatomical pathology results. This finding suggests that patient age cannot be used as one of the criteria in predicting the malignancy of thyroid nodules.

Gender was obtained from 71 research subjects, consisting of 16 men (22.5%) and 55 women (77.5%). Thyroid cancer is the fifth most common cancer in women in America [16]. Thyroid cancer is more common in women than men, with an approximate ratio of 3:1 [17,18]. Female gender was 903 subjects in 1113 patients with thyroid nodules and was found not to be associated with malignancy outcome [19]. Thyroid nodules are found to be 4 times more common in women than men [8]. Total 75% of cases occur in women and two-thirds of cases occur in people under 55 years of age [3]. Age is less than 20 or more than 70 years, and in some studies, it was found that the risk increased in men [7]. Meanwhile, according to Rahimi et al, in most studies, age and gender are not associated with malignancy [9]. This is consistent with this study, where the results of Chi-Square analysis found that there was no significant difference between gender and postoperative anatomical pathology results. This finding suggests that the sex of the patient cannot be used as one of the criteria in predicting the malignancy of thyroid nodules.

The prevalence of thyroid nodules palpable by physical examination is about 4-7% in women and 1% in men living in areas with sufficient iodine. By high-resolution ultrasound examination of the neck and thyroid thyroid nodules are detected in about 19% to 68% of randomly selected people, with a higher frequency occurring in women and the elderly [3]. Research by Triantafillou et al. 2018 also mentioned that nodules are found clinically in 5% of women and 1% of men in non-endemic areas and are not associated with malignancy [19]. Most patients with thyroid nodules in the study were recorded as having multiple nodules (MNT), as many as 42 people (59.2%), while the remaining 29 people (40.8%) had single nodules (SNT). The results of Chi-Square analysis showed that there was no significant difference between the number of nodules and postoperative anatomical pathology results. This finding indicates that the number of nodules cannot be used as one of the criteria in predicting the malignancy of thyroid nodules.

In this study, nodule size data were obtained with a median of 4 cm (range 1-13 cm) with the number of subjects who had nodules under 5 cm in size as many as 43 people 60.6%) and nodules ≥5 cm in size as many as 28 people (39.4%). According to research from Stang et al, the size of the nodule obtained malignancy of 24% in patients with a size of 4-5.9 cm and 57% in patients with thyroid nodules measuring 8-10 cm [7]. Meanwhile, according to Rahimi et al, thyroid nodule size should not be used as a criterion for malignancy and thyroid nodules of any size should be suspected of being malignant [9]. This is in line with this study where from the results of Chi-Square analysis it was found that there was no significant difference between nodule size and postoperative anatomical pathology results. This finding suggests that nodule size cannot be used as one of the criteria in predicting thyroid nodule malignancy.

In this study, lymph node enlargement was found in 41 (57.7%) people and the remaining 30 people (42.3%) did not show such enlargement. According to research by Shah et al, in some thyroid cancer patients, the only symptom is a lump in the neck which turns out to be metastasized lymph nodes [15]. From the data analysis in this study, it was found that enlarged lymph nodes had quite good diagnostic test results with a sensitivity of 74.3%, specificity of 58.3%, PPV 63.4%, and NPV 70%. Lymph node enlargement in this study is statistically significant to have a risk of malignancy according to the results of postoperative anatomical pathology by 4 times. The resulting score in the calculation is 4 point.

The results of ultrasound assessment based on benign TIRADS ACR (grades 1-3) were 54 people (76.1%) and malignant TIRADS ACR (grades 4-5). According to Wu et al, ultrasound assessment with TIRADS ACR has a good predictive value, namely with a negative predictive value (NPV) of 85.3% (p=0.034), a specificity test of 66% (p=0.001) and a positive predictive value (PPV) of 73.6%. [20]. Thyroid nodules are detected in about 19-68% of ultrasound results in screened populations [19]. In Aryanti's research (2022) found that ultrasound characteristics, age and physical examination were able to accurately predict thyroid cancer. The presentation of nodules classified as high risk according to TIRADS ACR was found to be around 20%-56.2% with a sensitivity value of 81%, specificity 64.4%, accuracy 44.7%, PPV 90.5% and NPV 68.8% [21]. The results of research conducted by Kim (2021) in 1036 patients with ACR-TIRADS thyroid nodules had a risk of malignancy in the

following categories: category 5 (59.3%); 4 (20.7%); 3 (11.0%); 2 (6.0%), and 1 (5.5%) [22]. For nodules with high suspicion of malignancy (category 4 or 5), the combined sensitivity and specificity were 0.84 and 0.64. This study found that ultrasound assessment based on TIRADS ACR has a diagnostic test of thyroid nodule malignancy with a high sensitivity of 91.4%, while the specificity value is 38.9%, PPV 59.3%, and NPV 82.4%. The results of ultrasound examination based on the division of TIRADS ACR are statistically significant and have a 6.8x risk of malignancy according to the results of postoperative anatomical pathology. The resulting value score for ultrasound based on the TIRADS ACR class in this study has a weight of 5.

The results of the FNAB examination in this study obtained subjects with benign Bethesda categories (Grades 1-4) as many as 58 people (77.5%) and malignant (grades 5-6) as many as 13 people (22.5%). FNAB examination is considered an effective method for diagnosing thyroid nodules with the accuracy of FNAB examination showing 62.2%, with a specificity of 62.5%, sensitivity of 61.2%, and a positive estimate value of 75% and a negative estimate of 47.6%. FNAB examination is cheaper, takes less time, does not require local anesthesia and is relatively safe [23]. However, because the FNAB procedure only uses a needle, the aspirate taken is very likely to not represent the entire thyroid nodule [24]. In this study, the results of the FNAB examination based on the division of Bethesda were statistically significant and had a risk of malignancy according to the results of postoperative anatomical pathology of 7.8 times. From the data analysis in this study, it was found that the FNAB results had diagnostic test results for malignancy with a high specificity of 94.4%%, while the sensitivity value was 31.4%, PPV 84.6%%, and NPV 58.6%. The score obtained in this study for FNAB based on bethseda has a bobor of 5 points.

The definitive diagnosis of thyroid nodules is by anatomical pathology biopsy examination of the surgical samples. This examination takes a long time of three to seven days. The sampling method is quite invasive and requires the use of anesthesia [19]. In this study, the results of postoperative PA in the benign category (50.7%) were experienced by 36 people, while the malignant category included the remaining 35 people (49.3%). Research Abdelkader (2018) who conducted tests on 100 subjects with thyroid nodules found 71 subjects with benign PA results and 39 subjects found malignant [13].

After obtaining diagnostic test results from physical examination of LNs, ultrasound with TIRADS ACR, and FNAB with bethesda grading, it was found that each diagnostic test has its own advantages and disadvantages. Ultrasound examination has high sensitivity with low specificity, while FNAB with bethesda grading has low sensitivity and high specificity. The researcher analyzed whether combining the three diagnostic tests could improve the overall sensitivity and specificity values.

In determining malignancy in thyroid nodules, it was found that each variable gave a similar weight, namely LNs enlargement contributed a score weight of 4 points, TIRADS ACR ultrasound contributed a score weight of 5 points and Bethesda FNAB contributed a score weight of 5 points. The diagnostic test accuracy of the combined score of these three factors obtained the best ROC curve analysis results at a cut off value of 7 with a sensitivity value of 77.1%, specificity of 75%, PPV 75%, and NPV 77.1%. From the analysis, it was found that enlarged LNs, ultrasound, and FNAB with a score value ≥7 had a high risk of 10.13 times showing a postoperative anatomical pathology picture with a malignancy result compared to a score value <7 (low risk), with a significant p <0.001 (95%CI 3.39-30.16). This score category is henceforth referred to as the "Thyroid Nodule Factor 3 Score" and can be seen in Table 9.

TABLE 9: Score 3 Thyroid Nodule Factor.

Score 3 Thyroid Nodule Factor	
Variables	**Score**
Enlargement of LNs	4
USG (TIRADS ACR)	5
FNAB (Bethesda)	5
Maximum Score	**14**
Recommendation	
Score ≥7	High Risk of Thyroid Nodule Malignancy
Score <7	Low Risk of Thyroid Nodule Malignancy

It was concluded that if a patient with a thyroid nodule has a total score equal to or above 7 then there is a high risk of thyroid nodule malignancy. This is obtained if at least two of the three factors, namely LNs enlargement, TIRADS ACR ultrasound, and Bethesda FNAB show malignant results. This score can be applied to the examination of patients with thyroid nodules in polyclinics, where patients are given a complete history and clinical examination.

In the clinical examination, LNs examination is performed where if LNs enlargement is found, the patient gets a score of 4, otherwise if there is no LNs enlargement, the patient does not get a score (0 points). Followed by an ultrasound examination with an assessment of the TIRADS ACR category, if a TIRADS ACR category of 4 to 5 is obtained, the patient gets a score of 5 points.

If the ultrasound examination results in TIRADS ACR categories 1 to 3, the patient does not get a score (0 points). The thyroid nodule suffered by the patient has a high risk of thyroid malignancy if from these two examinations the patient has received a total score of more than 7 points, so no FNAB examination is required. However, if the patient has a score of less than 7, then FNAB is required. If from the physical examination of enlarged LNs, ultrasound and FNAB the patient gets a total score of more than equal to 7 points, then the patient has a high risk of thyroid nodule malignancy with a sensitivity of 77.1% and a sensitivity of 75%. Conversely, if the patient scores less than 7 points on all three examinations , then the patient has a low risk of thyroid nodule malignancy.

CONCLUSION

Based on the results of the research and discussion, the following conclusions can be drawn:

(1) Clinical examination of enlarged lymph nodes, ultrasound results based on TIRADS categories, and fine-needle aspiration biopsy based on Bethesda categories have the diagnostic accuracy to determine malignancy in thyroid nodules.
(2) The number of nodules had statistically significant diagnostic test results with p=0.531, sensitivity 62.9%, specificity 44.4%, PPV 52.4%, and NPV 55.2%.
(3) Nodule size had statistically significant diagnostic test results with p=0.286, sensitivity 45.7%, specificity 66.7%, PPV 57.1%, and NPV 55.8%.
(4) Lymph node enlargement had statistically significant diagnostic test results with p 0.005, sensitivity 74.3%, specificity 58.3%, PPV 63.4%, and NPV 70%.
(5) Ultrasound assessment based on TIRADS ACR has a diagnostic test result of thyroid nodule malignancy with a high sensitivity of 91.4%, while the specificity value is low at 38.9%, PPV 59.3%, and NPV 82.4%.
(6) FNAB results based on the Bethesda category have high specificity diagnostic test results of 94.4%%, while the sensitivity value is 31.4%, PPV 84.6%%, and NPV 58.6%.
(7) The "3 Factor Score" scoring criteria was obtained to determine the malignancy of thyroid nodules with three factors assessed, namely LNs enlargement which contributed a score weight of 4 points, TIRADS ACR ultrasound results contributed a score weight of 5 points and Bethesda FNAB results contributed a score weight of 5 points.
(8) The three-factor scoring criteria with a cut off value of 7 had a significance of p<0.001 with a sensitivity value of 77.1% and specificity of 75% with a sensitivity value of 77.1%, specificity of 75%, PPV of 75%, and NPV of 77.1%.
(9) A score of ≥7 has a high risk of 10.13 times showing a postoperative anatomical pathology picture with a malignancy outcome compared to a score of <7 (low risk), significant p < 0.001 (95% CI 3.39-30.16).

Acknowledgments
All patients, all authors, and all support in papper

Declarations
Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by Udayana University/ Prof. Dr. I.G.N.G. Ngoerah Hospital Denapsar Bali.

REFERENCES

[1] Durante C, Costante G, Lucisano G, Bruno R, Meringolo D, Paciaroni A, et al. The Natural History of Benign Thyroid Nodules. JAMA 2015;313:926. https://doi.org/10.1001/jama.2015.0956.

[2] Carling T, Udelsman R. Thyroid Cancer. Annu Rev Med 2014;65:125–37. https://doi.org/10.1146/annurev-med-061512-105739.

[3] Chaigneau E, Russ G, Royer B, Bigorgne C, Bienvenu-Perrard M, Rouxel A, et al. TIRADS score is of limited clinical value for risk stratification of indeterminate cytological results. Eur J Endocrinol 2018;179:13–20. https://doi.org/10.1530/EJE-18-0078.

[4] Wisescistiati MV, Wetan NGAAMY, Manuaba IBTW, Adiputra PAT. Gambaran Pasien Karsinoma Tiroid Berdiferensiasi di RSUP Sanglah Tahun 2015-2020. JMU-Jurnal Medika Udayana ISSN: 2597-8012 2022;4:1–5.

[5] Wei Y, Zhou X, Liu S, Wang H, Liu L, Liu R, et al. Novel and Practical Scoring Systems for the Diagnosis of Thyroid Nodules. PLoS One 2016;11:e0163039. https://doi.org/10.1371/journal.pone.0163039.

[6] Li F, Chen G, Sheng C, Gusdon AM, Huang Y, Lv Z, et al. BRAFV600E mutation in papillary thyroid microcarcinoma: a meta-analysis. Endocr Relat Cancer 2015;22:159–68. https://doi.org/10.1530/ERC-14-0531.

[7] Stang MT, Carty SE. Recent developments in predicting thyroid malignancy. Curr Opin Oncol 2009;21:11–7. https://doi.org/10.1097/CCO.0b013e32831db2af.

[8] Zamora EA, Khare S, Cassaro S. Thyroid Nodule. StatPearls [Internet] https://WwwNcbiNlmNihGov/Books/NBK535422/ 2023.

[9] Rahimi M, Farshchian N, Rezaee E, Shahebrahimi K, Madani H. To differentiate benign from malignant thyroid nodule comparison of sonography with FNAC findings. Pak J Med Sci 2012;29. https://doi.org/10.12669/pjms.291.2595.

[10] Ugurlu S, Caglar E, Erdem Yesim T, Tanrikulu E, Can G, Kadioglu P. Evaluation of Thyroid Nodules in Turkish Population. Internal Medicine 2008;47:205–9. https://doi.org/10.2169/internalmedicine.47.0608.

[11] Zhang L, Wang Y, Li X, Wang Y, Wu K, Wu J, et al. Identification of a Recurrence Signature and Validation of Cell Infiltration Level of Thyroid Cancer Microenvironment. Front Endocrinol (Lausanne) 2020;11. https://doi.org/10.3389/fendo.2020.00467.

[12] Aryanti C, Sudarsa IW, Adiputra PAT, Setiawan IGB. The development of nomogram for predicting thyroid cancer in subject with single thyroid nodule in Bali, Indonesia. International Academic Research Journal of Surgery 2022;2:27–30. https://doi.org/10.47310/iarjs.2022.v02i01.007.

[13] Abdelkader AM, Zidan AM, Younis MT, Dawa SK. Preoperative Evaluation of Thyroid Nodules: A Prospective Study Comparing the accuracy of Ultrasound (TI-RADS) Versus the FNAC Bethesda System in Relation to the Final Postoperative Histo-pathological Diagnosis. Annals of Pathology and Laboratory Medicine 2018;5:A801-809. https://doi.org/10.21276/apalm.2110.

[14] Hughes DT, Haymart MR, Miller BS, Gauger PG, Doherty GM. The Most Commonly Occurring Papillary Thyroid Cancer in the United States Is Now a Microcarcinoma in a Patient Older than 45 Years. Thyroid 2011;21:231–6. https://doi.org/10.1089/thy.2010.0137.

[15] Shah JP. Thyroid carcinoma: epidemiology, histology, and diagnosis. Clin Adv Hematol Oncol 2015;13:3–6.

[16] Cabanillas ME, Dadu R, Hu MI, Lu C, Gunn GB, Grubbs EG, et al. Thyroid Gland Malignancies. Hematol Oncol Clin North Am 2015;29:1123–43. https://doi.org/10.1016/j.hoc.2015.07.011.

[17] Kumar M, Kumar A, Giri SS, Rabha D, Richa. Correlation of radiological parameters with cytological finding in the diagnosis of thyroid swelling. IP Archives of Cytology and Histopathology Research 2022;7:9–15. https://doi.org/10.18231/j.achr.2022.003.

[18] Boudina M, Katsamakas M, Chorti A, Panousis P, Tzitzili E, Tzikos G, et al. Diagnostic Accuracy of Ultrasound and Fine-Needle Aspiration Cytology in Thyroid Malignancy. Medicina (B Aires) 2024;60:722. https://doi.org/10.3390/medicina60050722.

[19] Triantafillou E, Papadakis G, Kanouta F, Kalaitzidou S, Drosou A, Sapera A, et al. Thyroid ultrasonographic charasteristics and Bethesda results after FNAB. Journal of BUON 2018;23:139–43. https://doi.org/10.1530/endoabs.56.p1120.

[20] Wu XL, Du JR, Wang H, Jin CX, Sui GQ, Yang DY, et al. Comparison and preliminary discussion of the reasons for the differences in diagnostic performance and unnecessary FNA biopsies between the ACR TIRADS and 2015 ATA guidelines. Endocrine 2019;65:121–31. https://doi.org/10.1007/s12020-019-01886-0.

[21] Trimboli P, Knappe L, Treglia G, Ruberto T, Piccardo A, Ceriani L, et al. FNA indication according to ACR-TIRADS, EU-TIRADS and K-TIRADS in thyroid incidentalomas at 18F-FDG PET/CT. J Endocrinol Invest 2020;43:1607–12. https://doi.org/10.1007/s40618-020-01244-2.

[22] Kim PH, Yoon HM, Hwang J, Lee JS, Jung AY, Cho YA, et al. Diagnostic performance of adult-based ATA and ACR-TIRADS ultrasound risk stratification systems in pediatric thyroid nodules: a systematic review and meta-analysis. Eur Radiol 2021;31:7450–63. https://doi.org/10.1007/s00330-021-07908-8.

[23] Rahmadhani S, Asri A, Tofrizal T. Akurasi Fine Needle Aspiration Biopsy sebagai Prosedur Diagnostik Nodul Tiroid di Laboratorium Patologi Anatomi Rumah Sakit Umun Pusat DR M Djamil Padang. Jurnal Kesehatan Andalas 2018;7:411. https://doi.org/10.25077/jka.v7i3.895.

[24] Choong KC, Khiyami A, Tamarkin SW, McHenry CR. Fine-needle aspiration biopsy of thyroid nodules: Is routine ultrasound-guidance necessary? Surgery (United States) 2018;164:789–94. https://doi.org/10.1016/j.surg.2018.04.047.